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(54) Title: LIPOPROTEINS AS NUCLEIC ACID VECTORS			
(57) Abstract			
<p>The present invention relates to materials and methods for the <i>in vivo</i> transport and delivery of nucleic acids. More particularly, it concerns the use of lipoproteins, including but not limited to, low density lipoproteins ("LDL"), and/or apolipoproteins for the binding and <i>in vivo</i> transport of nucleic acids. In addition, the present invention relates to the use of lipoproteins in the early detection of cancer and/or metastatic cancer and/or arteriosclerosis.</p>			

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**DESCRIPTION****LIPOPROTEINS AS NUCLEIC ACID VECTORS****BACKGROUND OF THE INVENTION**

The present application is a continuation-in-part of co-pending U.S. Patent Application  
5 Serial No. 08/874,807 Entitled "Lipoproteins As Nucleic Acid Vectors" filed June 13, 1997.  
The entire text of the above-referenced disclosure is specifically incorporated by reference  
herein without disclaimer.

**1. Field of the Invention**

The present invention relates to materials and methods for the *in vivo* transport and delivery of nucleic acids. More particularly, it concerns the use of lipoproteins, including but not limited to, low density lipoproteins ("LDL"), and/or apolipoproteins for the *in vivo* transport of nucleic acids. In addition, the present invention relates to the use of lipoproteins in the early detection of cancer and/or metastatic cancer and/or arteriosclerosis.

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**2. Description of Related Art**

The ultimate curative method for any genetic disorder, whether the disorder is inherited or results from a mutation, depends on an effective mode of replacing or augmenting non-functional gene(s). This process is now termed gene or genetic therapy. There are two  
20 important aspects to genetic therapy, the gene delivery system/vehicle and the gene control/expression program. Ideally, a replacement gene should become resident in the genome of the target cells/organism and be transferable to subsequent generations of cells and progeny, *i.e.*, the change is incorporated into the germ cells or reproductive cells, the sperm and ovary. Although there have been several significant breakthroughs in this field, this area of  
25 biotechnology is still in its early development phase. The first step in any approach to gene replacement is the delivery of the specific gene (nucleic acid) to the cells.

- 2 -

Many techniques have been and are being developed to deliver and express genes in cells and specific tissues in mammals *in vivo*. Several general, non-specific methods for delivering genes have been reported involving aerosol nucleic acid delivery to cells (Stribling *et al.*, 1992); calcium phosphate precipitation, using a steep change in ionic strength (Wigler *et al.*, 1979); DEAE-dextran (Sompayrac *et al.*, 1981); electroporation, forcing the nucleic acid into the cell by using an electric field or current (Neumann *et al.*, 1982); microinjection, physically injecting the nucleic acid into a cell (Benvenisty *et al.*, 1986; Wolff *et al.*, 1990); and polycationic molecules such as polylysine polypeptides (Curiel *et al.*, 1992) and cationic lipids (Lee *et al.*, 1996).

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Liposomes, vesicles composed of synthetic or non-natural lipids such as long-chain fatty adds. can be used to carry the nucleic acid into the cell cytoplasm non-specifically (Felgner *et al.*, 1987). A recent invention describes the delivery of a self-initiating and self-sustaining gene expression system which contains an RNA polymerase prebound to a DNA molecule using the 15 aforementioned nucleotide delivery systems (U.S. Patent No. 5,591,601).

Viral vectors in which specific nucleic acid sequences are incorporated into a neutralized or inactivated virus can use their viral entry mechanism to gain entry to the cell cytoplasm *via* specific cellular receptors to deliver nucleic acids (Schimotohono *et al.*, 1981). The use of 20 specific cellular receptors is apparently a more specific method for delivering genes. In this approach, the nucleic acid is bound either freely, through charge association, or alternatively it is chemically and non-reversibly conjugated to proteins with specific receptor proteins on the membrane of target cells for receptor-mediated uptake (Wu *et al.*, 1988, Wu *et al.*, 1989).

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Techniques such as calcium phosphate precipitation, electroporation or DEAE-dextran transfection are not suitable for *in vivo* applications. Bombarding cells with nucleic acids under high pressure is a technique which has very limited applications in that it can only be applied topically and only a small number of cells can be targeted. Microinjection of nucleic acids into cells is mainly performed *in vitro* and requires actively dividing cells.

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- 3 -

Gene delivery systems that use the viral entry mechanism of recombinant viral vectors have major disadvantages. Systems that utilize replication-defective adenoviral vectors can infect a wide variety of eukaryotic cell types including quiescent somatic cells utilizing the viral entry mechanism. However, adenoviral vector-based delivery systems are only successful in 5 transient gene expression and repeated administration of the viral vector results in a strong immunological response of the host. In addition, the host will experience an adenoviral infection and can experience its symptoms if the recombinant vector undergoes homologous recombination with the wild-type virus strain. Systems that employ recombinant retroviral vectors can be used for stable integration of the gene of interest into the host's genome, but only 10 actively dividing cells can be targeted. In addition, the disadvantages of the adenoviral vector systems also apply to retroviral vector systems (immune response, disease etc.).

Positively-charged polycationic molecules such as polylysine peptides which bind non-specifically to the negatively charged nucleic acids have been used to introduce DNA into the 15 chromosome of the recipient cell or organism. Cationic lipid vesicles, liposomes and micelles have been used in aggregates with DNA and viral envelope glycoproteins in non-specific delivery of genes. Liposomes, vesicles composed of synthetic or non-natural lipids, such as long-chain fatty acids, can be used to carry the nucleic acid into the cell cytoplasm non-specifically. In these systems, the liposomes are structured to "best fit" the nucleic acid and 20 insertion into the cell is through non-specific uptake.

The interaction of the liposomal delivery systems discussed above with the nucleic acid to be delivered is non-specific. In addition, prior art techniques are designed to deliver multiple copies of the nucleic acid to the cell cytoplasm. Optimally, however, only one or two copies of 25 a gene should be transfected per cell throughout the organism to replace a defective set of genes only in the specific cells and tissues where it would normally be expressed.

Thus there is a need for a safe and efficient gene delivery system that may be employed in the burgeoning field of gene therapy.

SUMMARY OF THE PRESENT INVENTION

The present invention contemplates a gene delivery system for use in gene therapy. Thus in particular embodiments, the present invention provides a composition comprising an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and a nucleic acid comprising an LDL or VLDL binding sequence, wherein the nucleic acid is bound to the polypeptide. In particularly preferred embodiments, the polypeptide comprises an LDL nucleic acid binding domain. In other embodiments, the polypeptide comprises a VLDL nucleic acid binding domain. In particular aspects of the present invention, the nucleic acid comprises an expression region operably linked to a promoter active in eukaryotic cells. In more particular embodiments, the expression region encodes a polypeptide. In other preferred embodiments, the expression region comprises an antisense construct.

In those embodiments in which the expression region encodes a polypeptide, the polypeptide may be selected from the group consisting of  $\alpha$ -globin,  $\beta$ -globin,  $\gamma$ -globin, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15,  $\beta$ -interferon,  $\gamma$ -interferon, cytosine deaminase, adenosine deaminase,  $\beta$ -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridyltransferase, glucocerbosidase, glucose-6-phosphatase, thymidine kinase, lysosomal glucosidase, growth hormone, nerve growth factor, insulin, adrenocorticotropic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor, thyroid stimulating hormone of CFTR, EGFR, VEGFR, IL-2 receptor, estrogen receptor, Bax, Bak, Bcl-X<sub>s</sub>, Bik, Bid, Bad, Harakiri, Ad E1B, an ICE-CED3 protease neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), retinoblastoma, insulin, mast cell growth factor, p53, p16, p21, MMAC1, p73, zac1 and BRCA1.

In those embodiments in which the expression region comprises an antisense construct, the antisense construct may be complementary to a segment of an oncogene. In more preferred embodiments, the oncogene may be selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.

- 5 -

The expression region may be linked to a promoter selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*,  $\beta$ -actin, human globin  $\alpha$ , human globin  $\beta$  and human globin  $\gamma$  promoter. In a defined embodiment, the nucleic acid binding domain is an apoB100 nucleic acid binding domain. In other embodiments, the composition of the present invention may further comprise one or more lipoproteins selected from the group consisting of apoA1, apoA-II, apoA-IV, acat, apoE, apoC-II, apoC-III and apo-D. In particularly preferred embodiment, the apoB100 is selected from the group consisting of human, rat and baboon apoB100.

In particular aspects of the invention, the polypeptide comprises at least two nucleic acid binding domains. In particularly preferred embodiments, the nucleic acid binding domain contains a motif selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motif and a nucleotide (ATP)-binding motif. In more defined embodiments, the binding domain may be selected from the group consisting of SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166 and SEQ ID NO:175.

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In other embodiments, the polypeptide may further comprise at least one nuclear localization sequence. More particularly, the nuclear localization sequence may be from apoB100. In more preferred embodiments, the nuclear localization sequence may be selected from the group consisting of SEQ ID NO:178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID

- 6 -

NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210.

Also contemplated by the present invention is a method for expressing a polypeptide in  
5 a human cell comprising the steps of providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) a nucleic acid comprising an expression cassette comprising a sequence encoding the polypeptide and a promoter active in eukaryotic cells, wherein the coding sequence is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; contacting the 10 composition with the cell under conditions permitting transfer of the composition into the cell; and culturing the cell under conditions permitting the expression of the polypeptide.

In particularly preferred embodiments, the polypeptide independently, is a tumor suppressor, a cytokine, an enzyme, a hormone, a receptor, or an inducer of apoptosis. In  
15 preferred embodiments, the tumor suppressor may be selected from the group consisting of p53, p16, p21, MMAC1, p73, zac1, BRCA1 and Rb. In preferred embodiments, the cytokine may be selected from the group consisting of IL-2, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, TNF, GMCSF,  $\beta$ -interferon and  $\gamma$ -interferon. In other preferred embodiments, the enzyme may be selected from the group consisting of cytosine 20 deaminase, adenosine deaminase,  $\beta$ -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerbosidase, glucose-6-phosphatase, thymidine kinase and lysosomal glucosidase. In still further preferred embodiments, the hormone may be selected from the group consisting of growth hormone, nerve growth factor, insulin, adrenocorticotropic hormone, parathormone, follicle-stimulating hormone, luteinizing 25 hormone, epidermal growth factor and thyroid stimulating hormone. In defined embodiments, the receptor may be selected from the group consisting of CFTR, EGFR, VEGFR, IL-2 receptor and the estrogen receptor. In other preferred embodiments, the inducer of apoptosis may be selected from the group consisting of Bax, Bak, Bcl-X<sub>s</sub>, Bik, Bid, Bad, Harakiri, Ad E1B and an ICE-CED3 protease.

- 7 -

In particularly preferred embodiments, the nucleic acid binding domain is an apoB100 nucleic acid binding domain. In more preferred embodiments, the apoB100 may be selected from the group consisting of human, rat and baboon low density apoB100. In still further preferred embodiments, the binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif. In particular embodiments, the polypeptide further may comprise at least one nuclear localization sequence. In especially preferred embodiments, the nuclear localization sequence is derived from an apoB100 nuclear localization sequence. In specific embodiments, the polypeptide may be selected from the group consisting of  $\alpha$ -globin,  $\beta$ -globin,  $\gamma$ -globin, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), and mast cell growth factor.

Also provided is a method for providing an expression construct to a human cell comprising providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; contacting the composition with the cell under conditions permitting transfer of the composition into the cell; and culturing the cell under conditions permitting the expression of the expression region.

In particularly preferred embodiments, the expression construct comprises an antisense construct. In more preferred embodiments, the antisense construct is derived from an oncogene. In exemplary embodiments, the oncogene may be selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*. In other embodiments, the expression construct comprises a nucleic acid coding for a gene. In preferred aspects the gene encodes a polypeptide.

In particularly preferred embodiments, the nucleic acid binding domain is an apoB100 nucleic acid binding domain. The apoB100 may be selected from the group consisting of human, rat and baboon low density apoB100. In other preferred embodiments, the DNA

binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.

5        Further the present invention contemplates a method for treating a human disease comprising providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; and administering the composition to a human subject having the disease under conditions permitting transfer of the composition into cells of the human subject.

15      In specific embodiments, the disease may be selected from the group consisting of cancer, diabetes, cystic fibrosis and arteriosclerosis. In preferred embodiments the polypeptide comprises at least two nucleic acid binding regions. In other preferred embodiments the polypeptide comprises at least one nuclear localization sequence. In particularly preferred embodiments, the nucleic acid encodes a gene. In other preferred embodiments, the expression construct comprises an antisense construct.

20      Another aspects of the present invention describes a pharmaceutical composition comprising an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and a nucleic acid comprising an LDL or VLDL binding sequence, wherein the nucleic acid is bound to the polypeptide; the pharmaceutical composition being dispersed in a suitable diluent.

25      Also contemplated by the present invention is a method of transforming a cell comprising providing a cell; contacting the cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the

- 9 -

promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; wherein expression of the expression region is indicative of the transformation.

Yet another aspect of the present invention contemplates a method of transfecting a cell comprising the steps of providing a cell; contacting the cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; wherein expression of the expression region is indicative of the transfection.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1A-FIG. 1C show the amino acid sequence of apoB-100.

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FIG. 2A-FIG. 2F is a homology alignment of SH3-like regions in apo B-100 with known SH3 domains of signal transduction proteins. FIG. 2A-FIG. 2D are the homology alignments and FIG. 2E and FIG. 2F identify the regions of apo B-100 and the proteins aligned.

- 10 -

FIG. 3A-FIG. 3D show a comparison of SH2-like regions in apo B-100 to known SH3 domains of signal transduction proteins. FIG. 3A-FIG. 3C are the homology alignments, FIG. 3D identifies the proteins and regions aligned.

5 FIG. 4A-FIG. 4C show a comparison of the apo B-100 SH 1-like region to SH1 kinase domains of known signal transduction proteins. FIG. 4A and FIG. 4B shows the alignments; FIG. 4C identifies the proteins and regions aligned.

10 FIG. 5A and FIG. 5B show the inter-kringle proline-rich regions of Apo[a] compared with the proline rich region of SH3-binding protein (3BP1). FIG. 5A shows the alignment; FIG. 5B identifies the proteins and regions aligned.

15 FIG. 6A and FIG. 6B show an homology alignment of specific regions of apo B-100 and the activation regions located at the amino- and carboxyl- termini of signal transduction proteins.

FIG. 7 illustrates the homology of specific regions of apo B-100 with proline pipe helix motifs of Tus.

20 FIG. 8A-FIG. 8D show a homology alignment among one region of the DNA-binding protein ISGF3 $\gamma$  and similar regions in apo B-100.

FIG. 9A-FIG. 9D show a homology alignment among regions of the DNA-binding protein ISGF3 $\gamma$  and similar regions in apo B-100.

25 FIG. 10A-FIG. 10N. FIG. 10N shows a sequence comparison of the DNA-binding domains of the SREBP1, SREBP2, and ADD1 proteins with similar regions found in apo B-100. FIG. 10B-FIG. 10N show a sequence comparison of the DNA-binding domains of SREBP1 with various apolipoproteins.

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- 11 -

FIG. 11 shows a comparison of the primary structures of known coiled-coil regions of DNA-binding proteins and analogous regions in apo B-100.

5 FIG. 12A-FIG. 12C show a comparison of known ATP-binding loop motifs to similar regions in apo B-100.

FIG. 13A-FIG. 13E show a comparison of known nuclear localization signal sequences to similar regions in apo B-100.

10 FIG. 14A-FIG. 14J show a comparison of human apo B-100 regions with sequenced regions of apo B-100 from other species.

15 FIG. 15 shows the composition of the LDL gene delivery system of the instant invention. LDL containing apo B-100 is depicted along with a DNA sequence containing a promoter, a protein coding region, a 3' untranslated region, and a non-coding region.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

20 The present invention arises from the discovery that regions of apolipoproteins, the protein fraction of lipoprotein particles, are similar in primary structure and amino acid sequence to cellular proteins which are known to bind to DNA. Presently, the only known functions of lipoproteins VLDL, IDL, LDL and HDL are the solubilization and transport of hydrophobic lipids in plasma. The instant invention shows that LDLs, but not other lipoproteins, form a complex with DNA.

25 Herein, synthetic analogues of regions of DNA have been shown to bind to highly purified preparations of human, rat, and baboon LDL but not to other human lipoproteins such as VLDL and HDL, nor to mouse lipoproteins. In fact, the differences observed among the four species tested suggests that human, rat, and baboon lipoproteins behave very similarly in terms of DNA binding preference. Further, purified preparations of human, rat, and baboon LDLs are shown to complex with the promoter region of the human cytomegalovirus. Thus, the present 30 invention demonstrates that human LDL complexes with specific regions of genomic DNA.

Because lipoproteins have specific cell membrane receptors and are actively and specifically internalized by many different cell types in mammals, and because the inventors show that LDL can bind DNA, these lipoproteins can be used as gene delivery vectors. More 5 specifically, this invention relates to materials and methods for the use of lipoproteins, such as LDL, or, for example, apolipoproteins such as, but not limited to, apoB-100, apoAI, apoE, apoAIV, and apoC, or more specifically still, the DNA binding regions of these lipoproteins, as gene delivery vectors *in vivo*. As explained in greater detail below, the various embodiments of 10 this invention include, but are not limited to, the delivery of nucleic acids to a cell in the form of an LDL-lipoprotein complex, the specific delivery of DNA to the nucleus, and the specific localization of delivered DNA to specific nuclear sites.

Plasma levels of DNA increase in a variety of chronic diseases including lupus erythematosus (Steinman, 1984), viral hepatitis (Neurath *et al.*, 1984), and a variety of cancers 15 (Leon *et al.*, 1977; Shapiro *et al.*, 1983; Stroun *et al.*, 1987; Nawroz *et al.*, 1996; Anker *et al.*, 1997; Chen *et al.*, 1996). It further has been shown that lipoproteins in the blood of non-tumor carrying organisms are not bound to nucleic acids. However, cancer-carrying individuals, and in particular individuals with metastatic cancers, release large amounts of nucleic acids, into 20 the blood. Thus, this invention also relates to the observation that lipoproteins in the blood of cancer patients and especially metastatic cancer patients are bound to nucleic acids, including DNA. Accordingly, this invention also may be used to provide a simple screening test for the presence or absence of cancer, especially metastatic cancer, by isolating a patient's lipoproteins and determining whether the lipoproteins are bound to nucleic acids; the presence of 25 lipoprotein-bound nucleic acid being correlative with the presence of cancer and/or metastatic cancer in the living body. Further embodiments of the present invention relate to the sequence specific detection of DNA bound to lipoproteins in a cancer patient as a method for the identification of specific types of cancer in a living body. These and other aspects of the present invention are discussed in greater detail below.

- 13 -

## 1. LIPOPROTEINS

Lipoproteins appear as micro-pseudomicellar particles in the blood plasma of all mammalian species including humans. Their major function is to transport lipids and other hydrophobic compounds (*i.e.*, fat-soluble vitamins) through the aqueous environment of the blood stream to their specific target cells. The transported lipids can be used as a major substrate for energy metabolism (*i.e.*, triglycerides), structural components for cell membranes (*i.e.*, phospholipids and cholesterol), or as precursors for steroid hormones and bile acids (*i.e.*, cholesterol). Although, lipoproteins vary widely in size and lipid content, they have a common general structure. Lipoprotein particles are believed to be spherical and consist of a hydrophobic core containing nonpolar lipids surrounded by a hydrophilic surface monolayer of polar lipids and proteins, which are called apolipoproteins.

Plasma lipoproteins may be separated into five major classes based on their density, size, and compositional and functional properties: 1) chylomicrons. 2) very low density lipoproteins (VLDL), 3) intermediate lipoproteins (IDL), 4) low density lipoproteins (LDL), and 5) high density lipoproteins (HDL). The different classes of lipoproteins show distinct compositional differences in apolipoprotein content. The specific role of each class of lipoproteins in lipid metabolism is determined by the interaction of these apolipoproteins with specific enzymes and cellular receptors.

### a. ApoB100 Structure and Function

The major protein constituent of LDL is apoB-100. ApoB-100 is one of two known natural ligands for the LDL (apoE/apoB) receptor which is found on the surface of a wide variety of mammalian cell types (Brown and Goldstein, 1986). LDLs are taken up by a process called receptor-mediated endocytosis (Brown and Goldstein, 1986). Hence, lipoproteins may be able to function as naturally-occurring liposomes which contain protein constituents that can bind specifically to nucleic acids and can be internalized by a wide variety of eukaryotic cell types *via* specific receptor mediated processes.

Human apolipoprotein B-100 (apoB-100) is a major apoprotein component of very-low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins

- 14 -

(LDL), and lipoprotein[a] (Lp[a]). ApoB-100 is synthesized and incorporated into VLDL and Lp[a] by the liver. Human LDL can be described as a spherical particle composed of a hydrophobic core of cholesterol esters and triglycerides encapsulated by an amphipathic monolayer of phospholipids, glycolipids and cholesterol in which the apoB-100 is partially imbedded (Myant, 1990). In addition to one molecule of apoB-100, LDL is known to contain varying numbers of apo C-I, apo C-II, apo C-III, apo E, and apo D (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994).

The primary structure of apoB-100, SEQ ID NO:1 (FIG. 1A-FIG. 1C) has been determined by amino acid sequence analysis (Yang *et al.*, 1986; Yang *et al.*, 1989) and inferred from its cDNA sequence (Yang *et al.*, 1986; Yang *et al.*, 1989; Knott *et al.*, 1986). There appear to be several different isoforms of apo B-100. The isoform shown in FIG. 1A-FIG. 1C is the isoform used for all of the alignments in the specification. Homologous regions in the other isoforms, however, would align similarly.

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The apparent molecular weight of apoB-100 is 512 kDa based on its amino acid composition of 4536 residues. The apoprotein contains 25 Cys residues (Coleman *et al.*, 1990; Yang, 1990), at least 16 of which form intramolecular disulfide bonds, with the remaining cysteines present as free sulphydryls, as additional (unassigned) intramolecular disulfides, or as intermolecular disulfide linkages to other apolipoproteins (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993). Several important functional regions on apoB-100 that have been identified include heparin-binding sites (Cardin *et al.*, 1987; Weisgraber and Rall, 1987), glycosylation sites (Knott *et al.*, 1986; Innerarity *et al.*, 1986), and the LDL receptor-binding region (Blanco-Vaca *et al.*, 1992, Knott *et al.*, 1986, Milne *et al.*, 1989).

25

ApoB-100, and apolipoprotein E (apoE), apolipoproteins present in the low-density lipoprotein group, function as ligands for the high-affinity receptor-mediated removal of certain lipoproteins from plasma by the liver and delivery of cholesterol and cholesterol esters to a variety of target tissues (Myant, 1990; Innerarity *et al.*, 1986; Brown and Goldstein, 1986; Mahley, 1988). A general mechanism for the receptor mediated uptake of LDL is well-

- 15 -

established (Myant, 1990; Innerarity *et al.*, 1986; Brown and Goldstein, 1986; Mahley, 1988), and the role of the apoB-100 molecule in this mechanism also is well defined.

Specific binding of low density lipoproteins to their mammalian cell receptors depends  
5 on the presence and conformation of the apoB-100 ligands (Kinoshita *et al.*, 1990). Several reports have shown that the interaction of apoB-100-lipoproteins with the up-regulated, high affinity LDL (apoB/apoE) receptor is modulated by the lipid composition of the particle (Teng *et al.*, 1985; Marcel *et al.*, 1988), by other apoproteins such as apo[a] in Lp[a] (Kostner and Grillhofer, 1991; Young *et al.*, 1986) and apoE in  $\beta$ -VLDL (Innerarity *et al.*, 1986; Mahley, 10 1988), and by monoclonal antibodies to specific regions of the apoB-100 molecule (Innerarity *et al.*, 1986; Young *et al.*, 1986).

In searching the apoB-100 sequence for regions of sequence similarity to other proteins, nucleic acid binding regions (deoxyribonucleic acids, DNA and ribonucleic acids, RNA),  
15 nucleotide-binding regions, and nuclear-localization regions in the amino acid sequence of apoB-100 and apoE, have been identified. The present invention demonstrates that highly purified preparations of human, rat, and baboon LDL bind specifically to pure preparations of human genomic DNA. These properties impart to the lipoproteins the capacity to serve as delivery vehicles for genetic material.

20 Lipoprotein particles carry a variety of vitamins and steroid compounds in their pseudo-micelle lipid core which may function in the control of gene expression. These attributes impart to the lipoproteins a virus-like character as well as capacity. While the inventors do not wish to be bound by any particular theory, the many control elements and signal motifs in the primary  
25 structure of the apolipoproteins are suggestive of the ability of these proteins to transport nucleic acids, enter the cell, participate in signal transduction, enter the nuclear space, initiate incorporation of nucleic acid materials into the resident genome, and cause its subsequent expression. As used herein, the term "primary structure" refers to the amino acid sequence of the protein. The capacity of purified LDL to bind to human genomic DNA, along with apoB-100's homology to SH1, SH2, and SH3 signal transducer domains supports this hypothesis.  
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- 16 -

These properties of apoB100, and methods of exploiting these properties, are discussed in further detail below.

## 2. NUCLEIC ACID BINDING REGIONS

5 The inventors have found that apo B-100 is also involved in DNA binding. DNA is the genetic blueprint that contains the information necessary for cell growth, differentiation, proliferation, and cellular response to environmental factors. The phenotypic differences between various cell types in higher eukaryotes are mainly due to differences in cellular gene expression.

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The regulation of gene expression is predominantly controlled at the stage of initiation of transcription and is mediated by proteins which recognize specific DNA sequences. In order to recognize and bind to a specific DNA sequence a protein utilizes a structural motif. Over the past 15 years, several structural DNA binding motifs have been identified including as zinc 15 fingers, helix-turn-helix, basic helix-loop-helix, KH RNA-binding motifs and leucine zippers and proline pipe helices. The inventors report here the identification of regions in apo B-100 with homology to various DNA binding motifs including: 1) Proline pipe helix DNA binding motifs, 2) ISGF3 $\gamma$ -like DNA binding motifs, 3) SREBP-like DNA binding motifs, 4) coiled-coil motifs, and 5) nucleotide (ATP)-binding motifs.

20

### a. Nucleotide and ATP Binding Motifs

The inventors discovered that there is a certain degree of homology between regions of apo B-100 and known ATP binding motifs found in other proteins including those involved in signal transduction and transcriptional-ribonucleotide synthesis (t-RNA synthetases).

25 Typically, these proteins contain sites which interact with different regions of the nucleotide, *i.e.*, negatively charged phosphate regions, the ribose (carbohydrate) hydroxyl groups, and the base. A second site binds to the substrate ligand such as any amino acid in the case of t-RNA synthetases and tyrosine, serine and threonine residues in the phosphorylation of proteins.

30 Examination of the apoB-100 primary structure reveals several regions which are similar in sequence to the known nucleotide and ATP binding motifs and are suggestive of a similar

- 17 -

function. For example, ATP-binding sites are known to contain an essential ATP-binding lysine residue. In *lyn*, the site is T<sub>269</sub>KVAVTLKPG (SEQ ID NO:54) and in *lyk*, it is D<sub>386</sub>KVAIKTIREG (SEQ ID NO:55). A similar region can be found in apoB-100, DLNAVANKIAD (SEQ ID NO:56). The similarity of this region in apo B-100 with the ATP-binding sites on known tyrosine-kinases suggests that apo B-100 can bind to the nucleic acid, 5 ATP.

A single ATP-binding region occurs between residues 3800 and 3840 which is located 10 in the kinase domain of apoB-100. The sequence of this region with known ATP-binding regions of kinases is shown in FIG. 12A-FIG. 12C. FIG. 12A-FIG. 12C show a comparison of known ATP-binding loop motifs to similar regions in apo B-100. Bold letters indicate 15 conserved amino acids, critical amino acids (H and K) are indicated by the #, "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the proteins, and identical amino acids between the sequences in "C" are listed below the alignment. Sequence identification numbers are listed in the right margin. The critical lysine residue is retained and the degree of similarity suggests a like function.

The ATP-binding motifs typical of t-RNA synthetases are characterized by the signature 20 sequence HIGH (histidine, isoleucine, glycine histidine) SEQ ID NO:177, and a second motif which contains a critical lysine residue. These motifs are located within 300 residues and occur as proximal loops on the surface of the protein molecule. Several analogues of this signature sequence occur in the apoB-100 sequence (see FIG. 7 and FIG. 12A-FIG. 12C). An extended comparison of apoB-100 regions which contain the HIGH signature sequence is made with the 25 tyrosyl-tRNA synthetase sequence shown in FIG. 12A-FIG. 12C.

25

**b. Proline Pipe Helix Structures**

The proline pipe helix is usually present in proteins that contain proline every fifth 30 position (Myant, 1990) in the amino acid sequence that is at least 20 residues long (PXXXXP)<sub>n</sub> (SEQ ID NO:75) where n>4. In the proline pipe helix, 5.56 residues are required to make one complete left handed helical turn. The proline pipe helix is stabilized by a hydrogen bonding network between the C=O groups of residues in positions i+ 1, i+2, i+3 (where i is a proline or

- 18 -

sometimes non-proline residue) with the NH groups in positions i+2, i+3, i+4, respectively, of the following turn (Blanco-Vaca *et al.*, 1992). The unusually large turn of the helix results in the formation of a channel running along the helix that is about 6Å in average diameter (Myant, 1990) and large enough to accommodate water (Blanco-Vaca *et al.*, 1992) and possibly other molecules.

One function of the proline pipe helix is DNA binding. For example, the proline pipe helix in *Tus* is involved in tight binding to highly specific 22-23 base pair DNA known as *Ter* sites (Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994). Because of its large diameter compared 10 to the  $\alpha$ -helix, the proline pipe helix spans the entire width of the major groove (Blanco-Vaca *et al.*, 1992) and results in a tight and highly specific fit. This tight fit also results in a high correspondence between the positively charged amino acid residues of the proline pipe helix and the negatively charged phosphate groups of DNA (Blanco-Vaca *et al.*, 1992). The occurrence of the proline pipe-DNA interactions in nature might be more widespread than 15 presently thought and this interaction might play a very important biological function.

Careful examination and analysis of the apoB-100 amino acid sequence shows that the 40-residue proline-rich segment P2682-I2719, or a portion of this segment, assumes a proline pipe helical conformation (see FIG. 7), PDFRLPEIAIPEFIPTLNLNDFQVPDLHIPEFQ 20 LPHISH (SEQ ID NO:76). Because the unique features of the proline pipe helix make it suitable for tight and highly specific DNA binding, this segment or motif in apoB-100 constitutes one of the DNA binding sites.

The functional implications of DNA binding by apoB-100 include, but are not limited 25 to: 1) binding of DNA such as, for example, microsatellite DNA (Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994) to apoB-100 or its fragment(s) for DNA transport from the cytoplasm to the nucleus; (2) binding of apoB-100 or its fragment(s) to the nuclear DNA to regulate transcription or effect other functions; or (3) binding of DNA to apoB-100 or its fragment(s) to transport DNA from the nucleus to the cytoplasm. Other functions as a consequence of apoB- 30 100 DNA binding through the apoB-100 proline pipe helix are not precluded. Therefore, the

- 19 -

proline pipe region of apoB-100 constitutes an important target for structure-based drug design and delivery systems.

5           c.     **ISGF3 $\gamma$ -like DNA binding motifs**

ISGF3 is a multimeric transcription factor involved in the regulation of transcription of a large set of genes. This factor dissociated into two protein components termed ISGF3 $\gamma$  and ISGF3 $\alpha$ . ISGF3 $\gamma$  is a 48 kDa protein that binds DNA recognizing the IFN-stimulated response element. ISGF3 $\alpha$  does not bind DNA. Regions in apoB-100 have been found to be homologous to the DNA-binding domain of ISGF3 $\gamma$  (FIG. 8A-FIG. 8D and FIG. 9A-FIG. 9D).

10           FIG. 8A-FIG. 8D show a homology alignment among one region of the DNA-binding protein ISGF3 $\gamma$  and similar regions in apo B-100. Basic amino acids are indicated in bold and \* indicates conserved amino acids between the two regions and V indicates conserved amino acids that have switched positions between the two sequences aligned. Sequence identification numbers are identified in the legend to the figure.

15           FIG. 9A-FIG. 9D show a homology alignment among regions of the DNA-binding protein ISGF3 $\gamma$  and similar regions in apo B-100. Basic amino acids are indicated in bold, "-" indicates gaps introduced in the sequence in order to align the two proteins. Sequence identification numbers are identified in the right margin.

20           This indicates apoB-100 can bind specific DNA sequences in a manner similar to ISGF3 $\gamma$ .

25           d.     **SREBP-Like DNA Binding Motifs**

Another region within apoB-100 shows striking resemblance to the DNA binding domains of previously identified sterol regulatory element binding proteins (SREBP's; FIG. 10A and FIG. 10B). A sequence comparison of the DNA-binding domains of the SREBP1, SREBP2, ADD1 proteins with similar regions found in apo B-100 are shown in FIG. 10A where basic amino acids are indicated in bold. "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino

- 20 -

acids between the two sequence are listed below the alignment. FIG. 10B shows a sequence comparison of the DNA-binding domains of SREBP1 with various apolipoproteins where basic amino acids are indicated in bold, "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins. V indicates conserved amino acids that have switched positions between the two sequences aligned, and identical amino acids between the two sequences are listed below the alignment. Sequence identification numbers are indicated in the legend to the figure. The full line of "\*\*\*\*\*" separates the different sequence alignments.

SREBP's are members of the basic helix-loop-helix-leucine zipper (bH-L-H-Zip) family of transcription factors and play a major role in the transcriptional regulation of a number of genes involved in cholesterol homeostasis as well as lipid biosynthesis. SREBP's contain 3 segments: 1) an NH<sub>2</sub> terminal bH-L-H-Zip DNA binding domain including an acidic transcription activating domain; 2) a middle segment containing two membrane spanning domains; and 3) a COOH terminal segment. In order for SREBP's to become functionally active transcription factors, their NH<sub>2</sub> terminal domain containing the bH-L-H-Zip region needs to be released from the endoplasmic reticulum or nuclear envelope. This process is mediated by a sterol-regulated protease. That apo B-100, like the SREBP's, binds DNA.

e. Coiled-coil Motif (Leucine Zipper)

The coiled-coil motif (Myant, 1990), sometimes referred to as the leucine zipper (Blanco-Vaca *et al.*, 1992), is characterized by two  $\alpha$ -helical chains that wrap around each other to form a left-handed supercoil. The amino acid sequence of coiled-coil forming proteins is characterized by the presence of heptad repeats, that is, three or more repeats of a seven-residue sequence where every third and every fourth position in the heptad is occupied by a hydrophobic residue (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994). The two  $\alpha$ -helical chains that form the coiled-coil can align either in parallel or anti-parallel orientation and their stabilities are dependent on the presence of strategically located hydrophobic and electrostatic interactions (Yang *et al.*, 1986; Yang *et al.*, 1989; Knott *et al.*, 1986; Coleman *et al.*, 1990; Yang, 1990; Cardin *et al.*, 1987; Weisgraber and Rall, 1987; Innerarity *et al.*, 1986; Milne *et al.*, 1989; Brown and Goldstein, 1986). The most attractive

- 21 -

feature of the coiled-coil is that highly specific interactions can be tailored by redesigning this relatively simple motif.

The coiled-coil motif occurs widely in native proteins (Lupas *et al.*, 1991; Cohen and Parry, 1986). It plays structural and functional roles in fibrous proteins such as keratin, myosin, elastin, fibrinogen, tropomyosin, etc. The coiled-coil motif also serves as the dimerization domain for a number of transcription factors such as GCN4 (O'Shea *et al.*, 1991; Ellenberger *et al.*, 1992), GAL4 (Kraulis *et al.*, 1992; Baleja and Sykes, 1991; Marmorstein *et al.*, 1992), c-Fos-c-Jun (Glover and Harrison, 1995), where only the dimeric form binds to DNA and is active. It is found in globular proteins, such as tRNA synthetase (Cusack *et al.*, 1990; Biou *et al.*, 1994), and serves as anchors into the tRNA. Naturally occurring coiled-coils can also be found as three-stranded (Bullough *et al.*, 1994a; Bullough *et al.*, 1994b) or four-stranded (Banner *et al.*, 1987) structures.

Sequence alignment analysis of apoB-100 predicts that there are at least eight coiled-coil structures of varying lengths in different regions of its amino acid sequence (FIG. 11). FIG. 11 shows a comparison of the primary structures of known coiled-coil regions of DNA-binding proteins and analogous regions in apo B-100. Bold letters indicate conserved amino acids. Sequence identification numbers are listed in the right margin.

While the inventors do not wish to be bound by any particular theory, it is likely that these coiled-coil domains play very important structural and functional roles that, in turn, are vital to the function of LDL. For example, the coiled-coil motif can serve as dimerization or multimerization sites that may be important in LDL solubilization or aggregation. The coiled-coil motif can also bind DNA, RNA or nucleotides and, therefore, plays a very important role in the regulation and energetics of protein synthesis. The coiled-coil motif can also serve as a template for transport of molecules within and between the cytoplasm and the nucleus. In addition, the coiled-coil motif can also serve as a (temporary) reservoir of ligands that may be important in the regulation of the metabolic pathways. This list is by no means exhaustive, but demonstrates the biological importance of the coiled-coil motif in apoB-100.

The discovery of the coiled-coil motif in apoB-100 and the important biological implications of its presence, apoB-100 by itself or as part of LDL, constitutes an important target for structure-based drug design, delivery, and diagnostic systems. Coiled-coil forming sequence in apoB-100 (as indicated in FIG. 11) can be used to design, study and manufacture 5 coiled-coil based peptide or protein delivery systems for drugs, radioisotopes, oligonucleotides, genes, antigens, antibodies, epitopes for vaccines, sugars, carbohydrate analogs and other ligands to specific targets in cells, tissues and organs. Either single strand or multiple strands of the apoB-100 coiled-coil forming peptide sequences that can be used as components of or attached to the aforementioned ligands either by covalent or non-covalent methods.

10 Coiled-coil forming sequences in apoB-100 (FIG. 11), or fragments, analogs, or modifications therefore can be used as site-specific targets for the delivery of drugs, radioisotopes, oligonucleotides, genes, antigens, antibodies, epitopes for vaccines, sugars, carbohydrate analogs and other ligands. Site-specific targeting includes the use of coiled-coils, 15 coiled-coil forming peptides, or any functional group that binds to the aforementioned coiled-coils sequences in apoB-100.

### 3. NUCLEAR LOCALIZATION SIGNALS

In addition to homology with DNA binding proteins, apoB-100 contains several regions 20 that are homologous to known nuclear localization signals (FIG. 13A-FIG. 13E). These signals include the NLS from human p53, Abl, and apoJ. FIG. 13A-FIG. 13E show a comparison of known nuclear localization signal sequences to similar regions in apo B-100.

The bipartite nuclear localization signal contains two essential elements comprised of 25 basic amino acids, H (histidine), R (Arginine), and K (Lysine) which are required for nuclear targeting. The signal motifs starts with two basic amino acids which are then followed by a ten to thirty amino acid spacer and a basic cluster of five amino acids three of which must be basic. Approximately 50% of the known nuclear proteins listed in the protein databases have this motif, while less than 5% of non-nuclear proteins have it. FIG. 13A and FIG. 13B show 30 sequences in apoB-100 with the perfect 10 amino acid spacer between the bipartite nuclear localization sequence element.

There is no strict requirement for the spacer length other than perhaps flexibility in the amino acids, *i.e.*, the dihedral angles. Indeed, there are basic amino acid clusters in the apo B-100 molecule that are separated by longer spacers and are nevertheless potential DNA-binding regions. FIG. 13C shows sequences in apoB-100 with more or less than 10 amino acids in the spacer region between the bipartite nuclear localization sequence element, and FIG. 13D-FIG. 13E show sequences in apoB-100 with more or less than 10 amino acids in the spacer region between an imperfect "bipartite" nuclear localization sequence element.

Thus, these regions in apoB-100 are NLS sequences capable of directing DNA to the nucleus of a cell. Apolipoproteins present on human LDL can bind to DNA through the DNA binding motifs identified herein. The functional bH-L-H-Zip domain within apoB-100 can enter the nucleus, following proteolytic release and/or aided by the nuclear localization signal domains present within the apolipoproteins, and regulate transcription of the target genes.

In addition, apo B-100 appears to be conserved across species. FIG. 14A-FIG. 14J show various regions of human apo B-100 aligned with the sequenced fragments of the apo B-100 from pig, rat, hamster, mouse, chicken and rabbit. Bold and underlined letters indicate positively charged, basic amino acids, and "-" indicates gaps introduced in the sequence in order to align the proteins:

#### 4. HOMOLOGY TO SIGNAL TRANSDUCING PROTEINS

The inventors have found that in addition to homology with nuclear localization signals and DNA binding proteins, apoB-100 molecule has regions of sequence similarity to known motifs in a variety of signal transduction molecules. For example, regions of apo B-100 are homologous to src homology 3 (SH3) (FIG. 2A-FIG. 2F), src homology 2 (SH2) (FIG. 3A-FIG. 3D) and src homology 1 (SH1) (FIG. 4A-FIG. C) kinase domains that are common to protein tyrosine kinases of the signal transduction system (Koch *et al.*, 1991; Pawson, 1992; Schlessinger, 1994; Margolis, 1992; Waksman *et al.*, 1993; Carpenter, 1992; Ugi *et al.*, 1994; Lowenstein *et al.*, 1992; Guevara, Jr. *et al.*, 1994), as well as activation regions located at the amino-and carboxyl- termini of signal transduction proteins (FIG. 6A and FIG. 6B).

- 24 -

FIG. 2A-FIG. 2F is a homology alignment of SH3-like regions in apo B-100 with known SH3 domains of signal transduction proteins, where "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, identical amino acids between the two sequences are listed below the alignment, and percent similarity is indicated in the right margin. This alignment is followed by a table identifying the regions of apoB-100 and the various proteins aligned to these regions along with their respective sequence identification numbers.

FIG. 3A-FIG. 3D show a comparison of SH2-like regions in apo B-100 to known SH3 domains of signal transduction proteins, where structurally important motifs are indicated by double underline, basic amino acids are indicated in bold, "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, identical amino acids between the two sequences are listed below the alignment, and percent similarity is indicated in the right margin. The alignment is followed by a table identifying the reference proteins and regions of apoB-100 in the alignment along with their sequence identification numbers.

FIG. 4 shows a comparison of the apo B-100 SH1-like region to SH1 kinase domains of known signal transduction proteins where basic amino acids are indicated in bold, "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino acids between the two sequences are listed above the alignment. The alignment is followed by a table identifying the reference proteins and the region of apoB-100 used for the alignment along with their respective sequence identification numbers.

FIG. 6A and FIG. B show a homolog alignment of specific regions of apo B-100 and the activation regions located at the amino- and carboxyl- termini of signal transduction proteins where "\*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino acids between the two sequences are listed above the alignment. Numbers in parenthesis indicate amino acid residues shown in the alignment and sequence identification numbers are listed in the right margin.

Discovery of these motifs in the apoB-100 sequences was based on a series of reports (Ye *et al.*, 1988; Trieu and McConathy, 1990; Trieu *et al.*, 1991) which showed that free proline inhibited binding of recombinant apo[a] to both Lp[a] and LDL. These results implied that proline within the apoB-100 sequence interacted with the kringle binding pocket. Molecular modeling was used to determine if proline is a ligand for the different apo[a] kringle types (Guevara, Jr. *et al.*, 1993). These studies concluded that although free proline can be accommodated by the ligand binding site of several apo[a] kringle types, proline located within a polypeptide chain probably does not fit into any of the ligand binding sites of apo[a] kringles. As an alternative possibility, proline might bind at an allosteric site on the kringle structure (Guevara, Jr. *et al.*, 1993), and thereby alter the ligand binding site of the kringle. A second possibility is that apo[a] kringles are not involved at all, but rather that the proline/threonine-rich inter-kringle regions (IKR's) associate with specific sites on apoB-100, and thereby enable recombinant apo[a] to bind to Lp[a] and LDL.

15

a. The SH3 Domain

The interkringle regions of Apo [a] have homology to 3BP1 (FIG. 5). FIG. 5 shows the inter-kringle proline-rich regions of Apo[a] compared with the proline rich region of SH3-binding protein (3BP1) where the conserved prolines are indicated in bold and "-" indicates gaps introduced in the sequences in order to align the two proteins. Following the alignments is a table identifying the inter-kringle proline-rich regions of Apo[a] and the proline-rich region of 3BP1 used for the alignment along with their respective sequence identification numbers.

Apo[a] is a hydrophilic, glycosylated apoprotein that is disulfide-linked to apo B-100 in the Lipoprotein[a] particle. The proline-rich hinge between kringle structures of the apo[a] are suggestive a of role in signaling. Cicchetti *et al.* (1992) and Ren *et al.* (1993) described a ten amino acid, proline-rich segment of the 3BP-1 protein which binds to an SH3 domain in Abl, a non-receptor protein tyrosine kinase involved in signal transduction. The proline-rich IKR's in apo[a] (McLean *et al.*, 1987; Guevara, Jr. *et al.*, 1992), like those in 3BP-1, contain the sequence PXP (SEQ ID NO:2) which is important for the interaction of these motifs with their corresponding SH3 domains.

Proline-rich binding proteins (BP's), SH3, and SH2 domains are regulatory domains in signaling proteins which mediate enzymatic activity, participate in intracellular protein-protein interactions, and bind to activated receptor protein-tyrosine kinases (Koch *et al.*, 1991; Pawson, 5 Schlessinger, 1994; Margolis, 1992; Waksman *et al.*, 1993; Carpenter, 1992; Ugi *et al.*, 1994; Lowenstein *et al.*, 1992; Guevara, Jr. *et al.*, 1994; Pleiman *et al.*, 1994). The sequence similarities noted between apo[a] IKR's and the proline-rich segment of 3BP-1 suggest a similar function for these regions of the apo[d] in non-covalent interactions between apo[a] and apoB-100, *i.e.*, binding of a proline-rich region in apo[a] to an SHB-like region in apoB-100.

In apoB-100, at least 13 regions share high sequence similarities with SH3 domains. SH3 domains are found in several signal transduction proteins such as phosphatidylinositol-3' kinase (PI3K) and the non-receptor tyrosine kinase Abl (see FIG. 1 and FIG. 4). This suggests that apo B-100 may have signal transduction properties.

**b. The SH2 Domain**  
Many signal transduction proteins and other proteins such as tyrosine phosphatases and tensin also contain SH2 domains (Koch *et al.*, 1991; Pawson, 1992; Schlessinger, 1994; Lowenstein *et al.*, 1992), often flanked by SH3 domains. SH2 domains are typically comprised of about 100 amino acids. In the signaling process, SH2 domains bind to specific phosphorytyrosine motifs of target proteins (Songyang *et al.*, 1993; Escobedo *et al.*, 1991). The apoB-100 sequence was examined for presence of SH2-like regions and numerous regions in the apoB-100 sequences were found to share some commonalties with SH2 domains of signaling proteins (FIG. 3A-FIG. 3D). This suggests that apoB-100 may interact with 20 phosphorylated proteins through SH2-like regions.

**c. The SH1 Domain**

Typically, signal transduction proteins also contain a kinase domain or src homology domain 1 (SH1) which is located in the carboxyl region of the protein and is comprised of about 30 300 amino acids (Rudd *et al.*, 1993). SH1 domains are highly homologous. Regions of apo B-100 have been found that share homology with SH1 domains (FIG. 4). In addition, apo B-100

shares homolog with the catalytic loop or active site motif in these signaling proteins. For example, the active site motif of *lyn* (EC 2.7.1.1 12) is R<sub>359</sub>KNYIHRDLRAAN (SEQ ID NO:52); a sequence that is highly conserved. An analogous region is found in apoB-100, K<sub>3919</sub>GTLAHRDFSAE (SEQ ID NO:53).

5 Furthermore, apo B-100 shares amino acid sequence homolog with the activation regions located at the amino- and carboxyl- termini of signal transduction proteins (FIG. 6A and FIG. 6B). Protein Kinase C and c-AMP-dependent kinase control sites are present at the amino-terminus of signal transduction proteins. Tyrosine kinase control sites are located in the carboxyl-terminus of these proteins. Typically, there is little sequence homology, at the amino-termini, but high homology is common at the carboxyl-termini of signaling protein kinases.

10

15 Regions of homology, within apo B-100 having sequence similarity to SH3, SH2 and SH1 domains and other cell signaling proteins, all point to the possibility that apo B-100 is involved in intracellular signaling.

## 5. PROTEIN EXPRESSION

As described above, the inventors have discovered that a particular region of the apoB-100 molecule is similar in sequence to the Steroid Regulatory Element Binding Proteins, SREBP1 and 2 and ADD1. Other regions of the apoB-100 molecule are similar to specific regions in other known DNA binding proteins including, but not limited to ISGF3γ, coiled-coil regions of GCN4 and hMLKI, and the proline-pipe sequences of Tus. Further, the inventors found that the amino acid sequence of apolipoproteins, such as apoB-100 have regions involved with nucleotide binding and nuclear localization. For example, apolipoproteins such as apoB-100 show homology to the SH1 kinase domains of protein tyrosine kinases and the HIGH and KMSK motif plus critical lysine of tRNA synthetases both known to bind ATP as well as to the basic helix-loop-helix motif of sterol regulatory element binding proteins (SREBPs) known to localize to the nucleus where they are involved in the regulation of transcription.

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a. Expression of apoB100

In certain embodiments of the present invention, it will be necessary to obtain apoB100 or lipoproteins containing apoB100 for use as DNA binding compositions. In particular embodiments as described herein below, such apoB100 may be obtained from the lipoprotein fraction of primate serum. As an alternative to purifying apoB100 from LDL fraction of serum, it is possible to generate pure fractions of apoB-100 by recombinant expression of the apoB100 gene. The apoB100 gene can be inserted into an appropriate expression system. The gene can be expressed in any number of different recombinant DNA expression systems to generate large amounts of the polypeptide product, which can then be purified and used as a DNA binding composition as described herein.

In one embodiment, specific amino acid sequence domains of an apoB100 polypeptide having for example, the sequence of SEQ ID NO:1, can be prepared. These may, for instance, be minor sequence variants of a polypeptide that arise due to natural variation within the population or they may be homologues found in other species. They also may be sequences that do not occur naturally but that are sufficiently similar that they function similarly and/or elicit an immune response that cross-reacts with natural forms of the polypeptide.

The nucleotide binding, nuclear localization and signal transduction domains of the apoB100 molecule are discussed in detail herein below. Recombinant technologies, well known to those of skill in the art, may be used to produce recombinant apoB100 with one or more of these domains having sequences that optimize the DNA binding and/or nuclear localization capacities of the molecule. Furthermore, in certain instances it may be necessary to "customize" such domains in order to increase binding to a particular DNA sequence whilst decreasing the binding to other sequences. Alternatively, it may be preferable to alter a particular apoB100 polypeptide, in order to decrease its binding affinity for a particular molecule. Accordingly, sequence variants of these domains can be prepared by standard methods of site-directed mutagenesis such as those described below in the following section.

- 29 -

Amino acid sequence variants of an apoB100 polypeptide, or particular domains therein can be substitutional, insertional or deletion variants. Deletion variants lack one or more residues of the native protein which are not essential for function or immunogenic activity.

5 Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide such as stability against proteolytic cleavage. Substitutions preferably are conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of:

10 alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine;

15 serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine.

Insertional variants include fusion proteins such as those used to allow rapid purification of the polypeptide and also can include hybrid proteins containing sequences from other proteins and polypeptides which are homologues of the polypeptide. For example, an insertional variant 20 could include portions of the amino acid sequence of the polypeptide from one species, together with portions of the homologous polypeptide from another species. Other insertional variants can include those in which additional amino acids are introduced within the coding sequence of the polypeptide. These typically are smaller insertions than the fusion proteins described above and are introduced, for example, into a protease cleavage site. Alternatively, insertional variants of the 25 present invention may be created in which one or more DNA binding domains and nuclear localization domain have been added to a native apoB100 molecule to alter particular characteristics of the molecule.

In one embodiment, major antigenic determinants of the polypeptide are identified by an 30 empirical approach in which portions of the gene encoding the polypeptide are expressed in a recombinant host, and the resulting proteins tested for their ability to elicit an immune response.

- 30 -

For example, PCR can be used to prepare a range of cDNAs encoding peptides lacking successively longer fragments of the C-terminus of the protein. The immunoprotective activity of each of these peptides then identifies those fragments or domains of the polypeptide that are essential for this activity. Further experiments in which only a small number of amino acids are removed at each iteration then allows the location of the antigenic determinants of the polypeptide.

Another embodiment for the preparation of polypeptides according to the invention is the use of peptide mimetics. Mimetics are peptide-containing molecules that mimic elements of protein secondary structure. See, for example, Johnson *et al.*, "Peptide Turn Mimetics" in *BIOTECHNOLOGY AND PHARMACY*, Pezzuto *et al.*, Eds., Chapman and Hall, New York (1993). The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular

- 31 -

interactions, such as those of antibody and antigen. A peptide mimetic is expected to permit molecular interactions similar to the natural molecule.

Successful applications of the peptide mimetic concept have thus far focused on mimetics of  $\beta$ -turns within proteins, which are known to be highly antigenic. Likely  $\beta$ -turn structure within an polypeptide can be predicted by computer-based algorithms as discussed above. Once the component amino acids of the turn are determined, peptide mimetics can be constructed to achieve a similar spatial orientation of the essential elements of the amino acid side chains.

Modification and changes may be made in the structure of a gene and still obtain a functional molecule that encodes a protein or polypeptide with desirable characteristics. The following is a discussion based upon changing the amino acids of a protein to create an equivalent, or even an improved, second-generation molecule. The amino acid changes may be achieved by change the codons of the DNA sequence, according to the following data.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid substitutions can be made in a protein sequence, and its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the DNA sequences of genes without appreciable loss of their biological utility or activity.

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte & Doolittle, 1982).

- 32 -

**TABLE 1**

Amino Acids			Codons
Alanine	Ala	A	GCA GCC GCG GCU
Cysteine	Cys	C	UGC UGU
Aspartic acid	Asp	D	GAC GAU
Glutamic acid	Glu	E	GAA GAG
Phenylalanine	Phe	F	UUC UUU
Glycine	Gly	G	GGA GGC GGG GGU
Histidine	His	H	CAC CAU
Isoleucine	Ile	I	AUA AUC AUU
Lysine	Lys	K	AAA AAG
Leucine	Leu	L	UUA UUG CUA CUC CUG CUU
Methionine	Met	M	AUG
Asparagine	Asn	N	AAC AAU
Proline	Pro	P	CCA CCC CCG CCU
Glutamine	Gln	Q	CAA CAG
Arginine	Arg	R	AGA AGG CGA CGC CGG CGU
Serine	Ser	S	AGC AGU UCA UCC UCG UCU
Threonine	Thr	T	ACA ACC ACG ACU
Valine	Val	V	GUU GUC GUG GUU
Tryptophan	Trp	W	UGG
Tyrosine	Tyr	Y	UAC UAU

It is accepted that the relative hydrophobic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like.

Each amino acid has been assigned a hydrophobic index on the basis of their hydrophobicity and charge characteristics (Kyte & Doolittle, 1982), these are: Isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9);

- 33 -

alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

5 It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.*, still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within  $\pm 2$  is preferred, those which are within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly  
10 preferred.

15 It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Patent 4,554,101, incorporated herein by reference, states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

20 As detailed in U.S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate ( $+3.0 \pm 1$ ); glutamate ( $+3.0 \pm 1$ ); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline ( $-0.5 \pm 1$ ); alanine (-0.5); histidine \*-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4).

25 It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent and immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$  is preferred, those that are within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

30 As outlined above, amino acid substitutions are generally based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing

characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

5           **b. apoB100 Variants**

In order to determine the optimal DNA-binding sequences, recombinant fragments of apoB-100 or other apolipoproteins may be used in mobility shift assays or other common protein-DNA interaction assays, including, but not limited to, methylation interference assays, DNase-I footprinting assays, UV-crosslinking assays, Biotin/Streptavidin affinity systems, or 10 screening expression libraries encoding DNA-binding proteins. The recombinant apolipoprotein fragments are expressed by cloning these cDNA fragments in commercially available eukaryotic expression vectors and employing recombinant DNA expression techniques well known to the art.

15           In addition, the recombinant fragments may be mutated by employing site-directed mutagenesis or oligonucleotide-directed mutagenesis techniques in order to improve their affinity for nucleic acids and used either in their original or mutated form. Mutations in the recombinant apolipoprotein fragments may include, but are not limited to, addition of endosomolytic and/or nuclear localization peptide sequences employing common recombinant 20 DNA technology. The recombinant protein fragments are prebound to the nucleic acids of interest prior to their reassembly into freshly isolated lipoproteins and subsequent transfection. Alternatively, they are reassembled into lipoproteins prior to *in vitro* nucleic acid binding and 25 subsequent transfection. Separation of protein-bound DNA from free DNA may be required prior to transfection and is accomplished by adsorption to nitrocellulose membranes or other common techniques including, but not limited to size-exclusion or density ultracentrifugation.

Site specific mutations can be made within the proposed DNA binding motifs or nuclear 30 localization signal sequences of the apolipoproteins described in this invention, in order to improve their homology with known DNA binding motifs (*e.g.*, SREBP-like DNA-binding motifs, ISGF3 $\gamma$ -like DNA-binding motifs) and nuclear localization signal sequences (*e.g.*, NLS from human p53, Ap 1, IGFBP-3, ir, and apo J). Specific mutations in the DNA sequences of

- 35 -

steroid regulatory elements (SRE) and IFN-stimulated response elements which affect the DNA-binding affinity of SREBP and ISGF3 $\gamma$ , respectively, have been described (Smith *et al.*, 1990; Briggs *et al.*, 1993; Wang *et al.*, 1993; Veals *et al.*, 1992).

5        Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent proteins or peptides, through specific mutagenesis of the underlying DNA. The technique further provides a ready ability to prepare and test sequence variants, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence change(s) into the DNA. Site-specific mutagenesis allows the production  
10      of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Typically, a primer of about 17 to 25 nucleotides in length is preferred, with about 5 to 10 residues on both sides of the junction of  
15      the sequence being altered.

In general, the technique of site-specific mutagenesis is well known in the art. As will be appreciated, the technique typically employs a bacteriophage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis  
20      include vectors such as the M13 phage. These phage vectors are commercially available and their use is generally well known to those skilled in the art. Double stranded plasmids are also routinely employed in site directed mutagenesis, which eliminates the step of transferring the gene of interest from a phage to a plasmid.

25       In general, site-directed mutagenesis is performed by first obtaining a single-stranded vector, or melting of two strands of a double stranded vector which includes within its sequence a DNA sequence encoding the desired protein. An oligonucleotide primer bearing the desired mutated sequence is synthetically prepared. This primer is then annealed with the single-stranded DNA preparation, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated  
30      strand.

- 36 -

sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected that include recombinant vectors bearing the mutated sequence arrangement.

5       The preparation of sequence variants of the selected gene using site-directed mutagenesis is provided as a means of producing potentially useful species and is not meant to be limiting, as there are other ways in which sequence variants of genes may be obtained. For example, recombinant vectors encoding the desired gene may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants.

10

## 6. PURIFICATION OF LIPOPROTEINS

The purification of plasma LDL involves obtaining a composition of Lp(a) and subjecting the composition to reductive cleavage in a manner that allows the formation of cleavage products apo (a) and apoB100. These products are then separated to yield purified apo B100. Plasma lipoproteins may be isolated using standard sequential flotation ultracentrifugation methods as described (Schumaker and Puppione, 1986).

### a. Purification of Lp(a)

Lp(a) is known to be made in the liver of primates. The LDL and VLDL in the plasma represents the primary source for the purification of Lp(a). Plasma may be collected from any primate source for the purposes of the invention, or indeed any other source suspected of possessing Lp(a). The Lp(a) component of the plasma can then be separated from other components of the plasma using ultracentrifugational flotation at a density of 1.21 g/mL for 20 hours at 50, 000rpm followed by affinity chromatography using lysine-Sepharose<sup>TM</sup>. Of course, the ultra centrifugational procedure is only exemplary and those of skill in the art will be able to vary them according to the particular equipment and study need without undue experimentation. The plasma may be supplemented with various inhibitors to prevent the Lp(a) from interacting with LDL components of the plasma.

30       Having separated Lp(a) from the other plasma components the Lp(a) sample is purified using affinity chromatography lysine-Sepharose<sup>TM</sup> chromatography. This separation is

- 37 -

described in detail in PCT publication WO 97/17371, specifically incorporated herein by reference.

In some cases, it is desirable to use a method other than lysine-Sepharose™ chromatography for the purification of Lp(a), in such instances other chromatographic methods such FPLC may be employed. Such methods are disclosed in Scaru *et al.* 1993, incorporated herein by reference, and may be used in conjunction with the present invention to purify apo B100 from Lp(a).

The product purity can be assessed by for example, mobility on. 1% agarose gels, Western blots of SDS PAGE, utilizing anti-LDL antibodies.

**b. Isolation of Apo B100 from Lp (a)**

*(i) using centrifugation*

Following the purification of Lp(a), the apoB100 may be separated from the apo A fraction of the Lpa complex using reductive cleavage.. The purified intact Lp(a) protein is subjected to reductive cleavage wherein a known volume of Lp(a) is incubated with a reductant. Exemplary reductants include homocysteine, N-acetyl cysteine, 2-mercaptoethanol, 3-mercaptopropionate, 2-aminoethanol, dithiothreitol, and DTE.

The reaction is incubated at room temperature for 10-20 minutes. This is followed by the addition of an inhibitor to prevent non-covalent, lysine mediated interactions between apo (a) and apoB100.  $\epsilon$ -Aminocaproic acid (EACA) may be used as such an inhibitor. substituted by other lysine analogues, for example, compounds such as trans 4(amino-methyl)-cyclohexanecarboxylic acid, N-acetyl-L-lysine, p-benzylamine sulfonic acid, hexylamine, benzamidine, benzylamine, L-proline. Of course these are only exemplary lysine analogues and those of skill in the art may use other lysine analogues to prevent interaction between apo (a) and apoB100 proteins. The reaction conditions are described in greater detail in PCT publication number WO 97/17371. Of course, the conditions for the separation of apo (a) from the reaction mixture using sucrose density ultracentrifugation is only exemplary, and other methods commonly used by those of skill in the art may be used.

5                   (ii)     Isolation Using Chromatographic Methods

As an alternative to the above methods for the isolation of apo B100 from Lp(a) chromatographic methods may be utilized as exemplified below.

5

*Heparin Sepharose™ Chromatography*

Lp(a) may be treated with a reducing agent in the presence of a lysine analogue. For the purposes of this invention the lysine analog is supplied to prevent the interaction of apo (a) with apoB100. The reducing agent is supplied to break the disulfide bond of Lp (a). Lysine analogs for this invention include but are not limited to compounds such as EACA. trans 4(amino-methyl)-cyclohexanecarboxylic acid. N-acetyl-L-lysine. p-benzylamine sulfonic acid, hexylamine, benzamidine, benzylamine, L-proline or any other lysine analogue known to the artisan skilled in the art may be used. Example of reducing agents that may be used in this invention include, but are not limited to, homocysteine, N-acetyl cysteine, 2-mercaptopropanoic acid, 3-mercaptopropionate, 2-aminoethanol, dithiothreitol, and DTE.

10

15

20

For example, the mixture of Lp (a), a reducing agent and a lysine analog is incubated for a suitable period of time in a suitable buffer of pH 7.4. A heparin-Sepharose™ column is equilibrated with a suitable buffer containing the lysine analog and the reducing agent. The mixture is applied to the equilibrated column, the column is washed with the same buffer and the first eluate is collected.

25

The first eluate from the column contains the apo (a) dissociated from Lp (a). The "free" apo (a) is dialyzed against an appropriate buffer. the dialysis product is pure apo (a) that may be freeze dried and stored at -20°C or used immediately. The column is further washed with the buffer for a total of three column volumes followed by 3 volumes of 2M NaCl in the buffer. The high salt concentration serves to dissociate the remaining unreacted Lp(a) and LDL containing apoB100 free of apo (a).

*Lysine-Sepharose™ Chromatography*

An alternative to heparin-Sepharose™ chromatography is lysine chromatography. In this type of separation, Lp(a) is treated with a suitable reducing agent and then applied to a lysine Sepharose™ column that has been equilibrated with a suitable buffer of pH 7.4 containing the reducing agent. The column is washed with the same buffer and the first volume of elute is collected. This fraction contains LDL dissociated from apo (a). Further details of this type of chromatography for separating apolipoproteins may be found in PCT Publication WO 97/17371.

**7. SCREENING NUCLEIC ACIDS THAT BIND LDL**

Specifically contemplated by the present inventors are chip-based DNA technologies such as those described by Hacia *et al.* (1996) and Shoemaker *et al.* (1996). Chip technologies may be used to present DNA arrays for screening.

In a first embodiment, chip technologies may be employed to synthesize a variety of DNAs in order to test for their binding to an LDL with a specific apoB100 binding region. Briefly, these techniques involve quantitative methods for analyzing large numbers of nucleic acids rapidly and accurately. By tagging genes with oligonucleotides or using fixed probe arrays, one can employ chip technology to segregate target molecules as high density arrays and screen these molecules on the basis of hybridization. See also Pease *et al.* (1994); Fodor *et al.* (1991).

Thus, the invention may be applied for the screening of nucleic acids that bind to apoB100 containing lipoproteins. The LDL polypeptide or fragment may be either free in solution, fixed to a support, expressed in or on the surface of a cell, for example a bacterial cell. Either the LDL polypeptide or the nucleic acid may be labeled, thereby permitting determining of binding to the DNA molecules.

In another embodiment, the assay may measure the inhibition of binding of LDL to a natural or artificial substrate or binding partner. Competitive binding assays can be performed in which one of the agents (LDL, binding partner or compound) is labeled. Usually, the

- 40 -

polypeptide will be the labeled species. One may measure the amount of free label versus bound label to determine binding or inhibition of binding.

Another technique for high throughput screening of compounds is described in WO 5 84/03564. Large numbers of small test nucleic acids (test compounds) are synthesized on a solid substrate, such as plastic pins or some other surface. Similarly, test compounds of the present invention are reacted with LDL and washed. Bound polypeptide is detected by various methods.

10 In an alternative embodiment, the invention may be applied for the screening for variants of apoB100 containing lipoproteins to determine a greater or lesser affinity for a particular type of nucleic acid. These screening methods would be similar to those described above, except that the LDL peptide variants will be presented as an array with the nucleic acid binding regions being used to probe the array. Currently, one of the most widely used 15 approaches for screening polypeptide libraries is to display polypeptides on the surface of filamentous bacteriophage (Smith, 1991; Smith, 1992). Ladner *et al.*, (U.S Patent No 5,403,484, specifically incorporated herein by reference) reported the display of proteins on the outer surface of a chosen bacterial cell, spore or phage, in order to identify and characterize binding proteins.

20 In an alternative embodiment, purified apoB100 or DNA-binding fragments thereof can be coated directly onto plates for use in the screening techniques. Alternatively, antibodies to the polypeptide can be used to immobilize the polypeptide to a solid phase. Also, fusion 25 proteins containing a DNA binding region (preferably a terminal region) may be used to link peptides to a solid phase. Once linked, randomly sheared genomic DNA, transcripts or randomly generated oligomers may be contacted with the bound peptides. Any bound nucleic acid fragments can be identified by PCR using random primers if they are large enough. In the case where random oligomers are used, the oligomers, in addition to the random region, may comprise built in primer binding sites that can be used to amplify an intervening random region, 30 thereby identifying the region binding to apoB100.

- 41 -

Thus, using the technologies described herein, it will be possible for one of skill in the art to screen for and isolate a variety of nucleic acids that bind to apoB100 and variants of apoB100 that exhibit nucleic acid binding capacity, including increased or decreased binding as compared to wild-type apoB100.

5

## 8. LDL-DNA COMPLEX FORMATION

In particular aspects of the present invention, lipoproteins are employed in order to transport DNA into cell *in vitro* and *in vivo*. In the present invention, optimal DNA/LDL binding has been established. In particular embodiments a 1:1 ratio of DNA:LDL protein molar ratio of 1:1 are incubated at 37 °C for 30 min in a buffered solution. An exemplary buffer may be 50 mM Tris-HCl at pH 7.4 containing 150 mM NaCl. and 10 mM MgCl<sub>2</sub>. The concentrations of DNA and LDL protein may range from the pmolar range to the μmolar range. In a preferred embodiment, 0.39 pmole DNA are incubated with 0.39 pmole LDL-protein.

15 The incubation conditions may be altered to increase or decrease the efficiency of DNA/LDL binding. For example the incubation may occur at temperatures ranging from 4°C to 50°C, thus it is contemplated that the reaction mixture may be incubated at 4°C, 6°C, 8°C, 10°C, 12°C, 14°C, 16°C, 18°C, 20°C, 22°C, 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, 46°C, 48°C, 50°C.

20

The time of incubation may be varied from as little as 10 minutes to as long as 5 hours. Thus it is well within the skill of one in the art to incubate the mixture for varying degrees of time.

25 Other embodiments contemplate varying the concentration of MgCl<sub>2</sub> in the media. Thus the MgCl<sub>2</sub> concentration may vary from 1mM to 100 mM. Thus, it is contemplated that the reaction mixture contains 5mM MgCl<sub>2</sub>, 10mM MgCl<sub>2</sub>, 12mM MgCl<sub>2</sub>, 15mM MgCl<sub>2</sub>, 20mM MgCl<sub>2</sub>, 30mM MgCl<sub>2</sub>, 35mM MgCl<sub>2</sub>, 40mM MgCl<sub>2</sub>, 50mM MgCl<sub>2</sub>, 60mM MgCl<sub>2</sub>, 65mM MgCl<sub>2</sub>, 70mM MgCl<sub>2</sub>, 80mM MgCl<sub>2</sub>, 90mM MgCl<sub>2</sub>, or 100mM MgCl<sub>2</sub>.

30

## 9. GENE DELIVERY AND EXPRESSION IN EUKARYOTIC CELLS

The gene delivery system of the instant invention can be used to express any gene of interest in eukaryotic cells. The gene or its cDNA sequence is cloned into a plasmid containing the specific lipoprotein binding sequences (including, but not limited to SRE, E/C, FAS) and/or any eukaryotic regulatory sequence (for example, but not limited to HCMV, or tyrosine kinase promoter region) using DNA cloning techniques well known to the art. The orientation, number and location of the lipoprotein binding sequences may vary within the nucleic acid vector, but should not interrupt the protein coding sequence of the gene of interest.

10 The gene delivery system of the instant invention (see FIG. 15) can be used to transfect eukaryotic cells either *in vivo* or *in vitro* with any expression vector containing one or more of the aforementioned lipoprotein binding sequences. Expression vectors are designed using recombinant DNA cloning techniques known to the art and generally include five components linked in the following 5' to 3' orientation: i) an eukaryotic promoter sequence, 2) a sequence encoding a 5' untranslated RNA (UTR) which may include a first intron sequence followed by a consensus Kozak sequence and an initiation ATG, 3) a protein coding sequence, 4) a 3' UTR, and 5) a cognate transcription terminator sequence.

15 Lipoproteins are isolated from blood in a manner similar to the previously described procedures (see, Example 1) and bound to the nucleic acids of interest in a manner similar to the previously described DNA binding protocol (see, Example 2). Separation of protein-bound DNA from free DNA may be required prior to transfection and can be accomplished by adsorption to nitrocellulose membranes or other techniques well known to the art including, but not limited to size-exclusion or density ultracentrifugation.

25

### a) Control Regions

In order for the gene delivery system of the present invention to effect expression of a transcript encoding a selected gene, the polynucleotides encoding these genes will be under the transcriptional control of a promoter. A "promoter" refers to a DNA sequence recognized by the synthetic machinery of the host cell, or introduced synthetic machinery, that is required to initiate the specific transcription of a gene. The phrase "under transcriptional control" means

- 43 -

that the promoter is in the correct location in relation to the polynucleotide to control RNA polymerase initiation and expression of the polynucleotide.

The term promoter will be used here to refer to a group of transcriptional control modules that are clustered around the initiation site for RNA polymerase II. Much of the thinking about how promoters are organized derives from analyses of several viral promoters, including those for the HSV thymidine kinase (tk) and SV40 early transcription units. These studies, augmented by more recent work, have shown that promoters are composed of discrete functional modules, each consisting of approximately 7-20 bp of DNA, and containing one or more recognition sites for transcriptional activator or repressor proteins.

At least one module in each promoter functions to position the start site for RNA synthesis. The best known example of this is the TATA box, but in some promoters lacking a TATA box, such as the promoter for the mammalian terminal deoxynucleotidyl transferase gene and the promoter for the SV40 late genes, a discrete element overlying the start site itself helps to fix the place of initiation.

Additional promoter elements regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the tk promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

The particular promoter that is employed to control the expression of a therapeutic gene is not believed to be critical, so long as it is capable of expressing the polynucleotide in the targeted cell. Thus, where a human cell is targeted, it is preferable to position the polynucleotide coding region adjacent to and under the control of a promoter that is capable of

- 44 -

being expressed in a human cell. Generally speaking, such a promoter might include either a human or viral promoter.

In preferred embodiments, the human cytomegalovirus (CMV) immediate early gene 5 promoter, the SV40 early promoter and the Rous sarcoma virus long terminal repeat can be used to obtain high-level expression of the polynucleotide of interest. The use of other viral or mammalian cellular or bacterial phage promoters which are well-known in the art to achieve expression of polynucleotides is contemplated as well, provided that the levels of expression are sufficient to produce a growth inhibitory effect.

10 By employing a promoter with well-known properties, the level and pattern of expression of a polynucleotide following transfection can be optimized. For example, selection of a promoter which is active in specific cells, such as tyrosinase (melanoma), alpha-fetoprotein and albumin (liver tumors), CC10 (lung tumor) and prostate-specific antigen (prostate tumor) 15 will permit tissue-specific expression of the therapeutic gene.

Enhancers were originally detected as genetic elements that increased transcription from 20 a promoter located at a distant position on the same molecule of DNA. This ability to act over a large distance had little precedent in classic studies of prokaryotic transcriptional regulation. Subsequent work showed that regions of DNA with enhancer activity are organized much like 25 promoters. That is, they are composed of many individual elements, each of which binds to one or more transcriptional proteins.

The basic distinction between enhancers and promoters is operational. An enhancer 25 region as a whole must be able to stimulate transcription at a distance; this need not be true of a promoter region or its component elements. On the other hand, a promoter must have one or more elements that direct initiation of RNA synthesis at a particular site and in a particular orientation, whereas enhancers lack these specificities. Promoters and enhancers are often overlapping and contiguous, often seeming to have a very similar modular organization.

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- 45 -

Additionally, any promoter/enhancer combination (as per the Eukaryotic Promoter Data Base EPDB) could be used to drive expression of a particular construct. Use of a T3, T7 or SP6 cytoplasmic expression system is another possible embodiment. Eukaryotic cells can support cytoplasmic transcription from certain bacteriophage promoters if the appropriate bacteriophage polymerase is provided, either as part of the delivery complex or as an additional genetic expression vector.

According to the present invention, a number of different promoters are required. It is contemplated that these promoters may be the same or different, but the selection of particular 10 promoters for particular uses may be advantageous.

**b) IRES**

In certain embodiments of the invention, the use of internal ribosome binding site (IRES) elements may prove advantageous in accordance with the present invention. These 15 elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described (Pelletier and Sonenberg, 1988), as well an IRES from a mammalian message (Macejak and Sarnow, 1991). 20 IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message.

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Any heterologous open reading frame can be linked to IRES elements. This includes genes for secreted proteins, multi-subunit proteins, encoded by independent genes, intracellular or membrane-bound proteins and selectable markers. In this way, expression of several proteins can be simultaneously engineered into a cell with a single construct and a single selectable 30 marker.

In addition, it may be desirable to include polyadenylation signals in the vectors. These signals serve to terminate transcription and to stabilize mRNA transcripts produced from the vectors. A preferred polyadenylation signal is an SV40 polyadenylation signal.

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### c) Genes

The present invention contemplates the use of a variety of different genes inserted into the SV40 vector. For example, genes encoding enzymes, hormones, cytokines, oncogenes, receptors, tumor suppressors, transcription factors, drug selectable markers, toxins and various antigens are contemplated as suitable genes for use according to the present invention. In 10 addition, antisense constructs derived from oncogenes are other "genes" of interest according to the present invention.

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A common gene currently being used in many gene therapy trials is p53, which currently is recognized as a tumor suppressor gene. High levels of mutant p53 have been found in many cells transformed by chemical carcinogenesis, ultraviolet radiation, and several viruses. The p53 gene is a frequent target of mutational inactivation in a wide variety of human tumors and is already documented to be the most frequently-mutated gene in common human cancers. It is mutated in over 50% of human NSCLC (Hollstein *et al.*, 1991) and in a wide spectrum of other tumors. Overexpression of wild-type p53 has been shown in some cases to be anti-proliferative in human tumor cell lines. Thus, p53 can act as a negative regulator of cell growth (Weinberg, 1991) and may directly suppress uncontrolled cell growth or indirectly activate genes that suppress this growth. It has also been reported that transfection of DNA encoding wild-type p53 into cancer cell lines restores growth suppression control in such cells (Casey *et al.*, 1991; Takahasi *et al.*, 1992). It is thus proposed that the treatment of p53-associated cancers with wild type p53 in the compositions of the present invention will reduce the number of malignant cells or their growth rate.

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p16<sup>INK4</sup> belongs to a newly described class of CDK-inhibitory proteins that also includes p16<sup>B</sup>, p21<sup>WAF1</sup>, and p27<sup>KIP1</sup>. The p16<sup>INK4</sup> gene maps to 9p21, a chromosome region frequently deleted in many tumor types. Homozygous deletions and mutations of the p16<sup>INK4</sup> gene are frequent in human tumor cell lines. This evidence suggests that the p16<sup>INK4</sup> gene is a tumor

suppressor gene. This interpretation has been challenged, however, by the observation that the frequency of the p16<sup>INK4</sup> gene alterations is much lower in primary uncultured tumors than in cultured cell lines (Caldas *et al.*, 1994; Cheng *et al.*, 1994; Hussussian *et al.*, 1994; Kamb *et al.*, 1994; Kamb *et al.*, 1994; Mori *et al.*, 1994; Okamoto *et al.*, 1994; Nobori *et al.*, 1995; Orlow *et al.*, 1994; Arap *et al.*, 1995). Restoration of wild-type p16<sup>INK4</sup> function by transfection with a plasmid expression vector reduced colony formation by some human cancer cell lines (Okamoto, 1994; Arap, 1995).

Cell adhesion molecules, or CAM's are known to be involved in a complex network of molecular interactions that regulate organ development and cell differentiation (Edelman, 1985). Recent data indicate that aberrant expression of CAM's maybe involved in the tumorigenesis of several neoplasms: for example, decreased expression of E-cadherin, which is predominantly expressed in epithelial cells, is associated with the progression of several kinds of neoplasms (Edelman and Crossin, 1991; Frixen *et al.*, 1991; Bussemakers *et al.*, 1992; Matsura *et al.*, 1992; Umbas *et al.*, 1992). Also, Giancotti and Ruoslahti (1990) demonstrated that increasing expression of  $\alpha_5\beta_1$  integrin by gene transfer can reduce tumorigenicity of Chinese hamster ovary cells *in vivo*. C-CAM now has been shown to suppress tumors growth *in vitro* and *in vivo*. Thus, the compositions of the present invention can be employed to mediated C-CAM suppression of tumor cell growth.

Other tumor suppressors that may be employed according to the present invention include RB, APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, zac1, p73, VHL, MMAC1, FCC and MCC. Inducers of apoptosis, such as Bax, Bak, Bcl-X<sub>s</sub>, Bik, Bid, Harakiri, Ad E1B, Bad and ICE-CED3 proteases, similarly could find use according to the present invention.

Various enzyme genes are of interest according to the present invention. Such enzymes include cytosine deaminase, hypoxanthine-guanine phosphoribosyltransferase, galactose-1-phosphate uridylyltransferase, phenylalanine hydroxylase, glucocerbosidase, sphingomyelinase,  $\alpha$ -L-iduronidase, glucose-6-phosphate dehydrogenase, HSV thymidine kinase and human thymidine kinase.

In another example, the expression vector may include a nucleotide sequence encoding for functional apolipoprotein A-I for the prevention or treatment of atherosclerosis. Atherosclerosis is a disease that is characterized by the development of atherosclerotic lesions which contain cholesterol esters and other lipids that are derived from the blood circulation.

5 The plasma concentration of HDL is inversely correlated with the risk for development of atherosclerosis. HDL present in the blood circulation take up free cholesterol from extrahepatic cells which through the action of LCAT (lecithin-cholesterol acyltransferase) is converted to cholesterol esters and stored in the core of the HDL particles. The HDL cholesterol esters are transported either directly or indirectly *via* transfer to triglyceride rich lipoproteins (*i.e.*, VLDL,

10 IDL, LDL) to the liver by a process called "reverse cholesterol transport". Reverse cholesterol transport is of great importance for maintaining cholesterol homeostasis since the liver is the major organ for cholesterol excretion from the body *via* bile acids. Apo A-I is the major protein constituent of HDL and a cofactor LCAT. Therefore, increasing the plasma concentration of apo A-I containing HDL can increase the reverse cholesterol transport and reduce the risk for

15 atherosclerosis.

Hormones are another group of gene that may be used in the SV40 vectors described herein. Included are growth hormone, prolactin, placental lactogen, luteinizing hormone, follicle-stimulating hormone, chorionic gonadotropin, thyroid-stimulating hormone, leptin, adrenocorticotropin (ACTH), angiotensin I and II,  $\beta$ -endorphin,  $\beta$ -melanocyte stimulating hormone ( $\beta$ -MSH), cholecystokinin, endothelin I, galanin, gastric inhibitory peptide (GIP), glucagon, insulin, lipotropins, neuropeptides, somatostatin, calcitonin, calcitonin gene related peptide (CGRP),  $\beta$ -calcitonin gene related peptide, hypercalcemia of malignancy factor (1-40), parathyroid hormone-related protein (107-139) (PTH-rP), parathyroid hormone-related protein (107-111) (PTH-rP), glucagon-like peptide (GLP-1), pancreastatin, pancreatic peptide, peptide YY, PHM, secretin, vasoactive intestinal peptide (VIP), oxytocin, vasopressin (AVP), vasotocin, enkephalinamide, metorphinamide, alpha melanocyte stimulating hormone (alpha-MSH), atrial natriuretic factor (5-28) (ANF), amylin, amyloid P component (SAP-1), corticotropin releasing hormone (CRH), growth hormone releasing factor (GHRH), luteinizing hormone-releasing hormone (LHRH), neuropeptide Y, substance K (neurokinin A), substance P and thyrotropin releasing hormone (TRH).

Other classes of genes that are contemplated to be inserted into the SV40 vectors of the present invention include interleukins and cytokines. Interleukin 1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF and G-CSF.

5 Other therapeutics genes might include genes encoding antigens such as viral antigens, bacterial antigens, fungal antigens or parasitic antigens. Viruses include picornavirus, coronavirus, togavirus, flavivirus, rhabdovirus, paramyxovirus, orthomyxovirus, bunyavirus, arenavirus, reovirus, retrovirus, papovavirus, parvovirus, herpesvirus, poxvirus, hepadnavirus, 10 and spongiform virus. Preferred viral targets include influenza, herpes simplex virus 1 and 2, measles, small pox, polio or HIV. Pathogens include trypanosomes, tapeworms, roundworms, helminths. Also, tumor markers, such as fetal antigen or prostate specific antigen, may be targeted in this manner. Preferred examples include HIV env proteins and hepatitis B surface antigen. Administration of a vector according to the present invention for vaccination purposes 15 would require that the vector-associated antigens be sufficiently non-immunogenic to enable long term expression of the transgene, for which a strong immune response would be desired. Preferably, vaccination of an individual would only be required infrequently, such as yearly or biennially, and provide long term immunologic protection against the infectious agent.

20 In yet another embodiment, the heterologous gene may include a single-chain antibody. Methods for the production of single-chain antibodies are well known to those of skill in the art. The skilled artisan is referred to U.S. Patent No. 5,359,046, (incorporated herein by reference) 25 for such methods. A single chain antibody is created by fusing together the variable domains of the heavy and light chains using a short peptide linker, thereby reconstituting an antigen binding site on a single molecule.

Single-chain antibody variable fragments (Fvs) in which the C-terminus of one variable domain is tethered to the N-terminus of the other via a 15 to 25 amino acid peptide or linker, have been developed without significantly disrupting antigen binding or specificity of the 30 binding (Bedzyk *et al.*, 1990; Chaudhary *et al.*, 1990). These Fvs lack the constant regions (Fc) present in the heavy and light chains of the native antibody.

- 50 -

Antibodies to a wide variety of molecules are contemplated, such as oncogenes, toxins, hormones, enzymes, viral or bacterial antigens, transcription factors or receptors.

5           d.     **Antisense**  
The instant invention can be used to transfect eukaryotic cells with ribonucleotide sequences including anti-sense RNA and ribozymes, that function to inhibit the translation of any mRNA of interest, either by direct binding (to the mRNA of interest), or blocking deoxyribonucleic acid (DNA) coding sequences preventing transcription.

10           Anti-sense RNA inhibits the translation of mRNA by direct binding to the mRNA of interest and preventing protein translation, either by inhibition of ribosome binding or the translocation of the targeted mRNA molecule which then becomes more susceptible to nuclease degradation.

15           Antisense methodology takes advantage of the fact that nucleic acids tend to pair with "complementary" sequences. By complementary, it is meant that polynucleotides are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules. That is, the larger purines will base pair with the smaller pyrimidines to form combinations of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. Inclusion of less common bases such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others in hybridizing sequences does not interfere with pairing. Oncogenes such as *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl* also are suitable targets for antisense constructs.

20           Targeting double-stranded (ds) DNA with polynucleotides leads to triple-helix formation; targeting RNA will lead to double-helix formation. Antisense polynucleotides, when introduced into a target cell, specifically bind to their target polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene

- 51 -

transcription or translation or both within a host cell, either *in vitro* or *in vivo*, such as within a host animal, including a human subject.

Antisense constructs may be designed to bind to the promoter and other control regions, 5 exons, introns or even exon-intron boundaries of a gene. It is contemplated that the most effective antisense constructs will include regions complementary to intron/exon splice junctions. Thus, it is proposed that a preferred embodiment includes an antisense construct with complementarity to regions within 50-200 bases of an intron-exon splice junction. It has been observed that some exon sequences can be included in the construct without seriously affecting 10 the target selectivity thereof. The amount of exonic material included will vary depending on the particular exon and intron sequences used. One can readily test whether too much exon DNA is included simply by testing the constructs *in vitro* to determine whether normal cellular function is affected or whether the expression of related genes having complementary sequences is affected.

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As stated above, "complementary" or "antisense" means polynucleotide sequences that are substantially complementary over their entire length and have very few base mismatches. For example, sequences of fifteen bases in length may be termed complementary when they have complementary nucleotides at thirteen or fourteen positions. Naturally, sequences which 20 are completely complementary will be sequences which are entirely complementary throughout their entire length and have no base mismatches. Other sequences with lower degrees of homology also are contemplated. For example, an antisense construct which has limited regions of high homology, but also contains a non-homologous region (*e.g.*, ribozyme) could be designed. These molecules, though having less than 50% homology, would bind to target 25 sequences under appropriate conditions.

It may be advantageous to combine portions of genomic DNA with cDNA or synthetic sequences to generate specific constructs. For example, where an intron is desired in the ultimate construct, a genomic clone will need to be used. The cDNA or a synthesized 30 polynucleotide may provide more convenient restriction sites for the remaining portion of the construct and, therefore, would be used for the rest of the sequence.

e. Ribozymes

Ribozymes are RNA molecules that catalyze the specific cleavage of RNA. Ribozyme activity is mediated through the hybridization of the ribozyme molecule to a specific sequence in the target RNA, followed by the endonucleolytic cleavage of the target RNA within that sequence. Potential RNA cleavage sites can be identified by searching for specific ribonucleotide sequences that include sequences such as GUU, GUC, and GUA within the target RNA. Hammerhead motif ribozyme molecules can then be designed that contain short RNA sequences (15-25 ribonucleotides) that are complementary to the region including the cleavage site of the target RNA.

Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cook, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cook *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cook *et al.*, 1981). For example, U.S. Patent No. 5,354,855 reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cell lines to which they were applied; the altered genes included the oncogenes H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

- 53 -

Since the secondary structure of both target RNA as well as the anti-sense RNA is of great importance for the hybridization of both molecules, the predicted structural features can be analyzed and RNase protection assays can be used to determine hybridization efficiency. Anti-sense RNA and ribozymes can be synthesized employing chemical nucleic acid synthesis techniques well known to the art (*i.e.*, solid phase phosphoramidite synthesis) or the RNA molecules can be produced by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA. DNA sequences encoding ribozymes or anti-sense RNA may be incorporated into an expression vector. The expression vector may be prebound to purified plasma lipoprotein fractions prior to transfection into eukaryotic cells.

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**f. Self-initiating and self-sustaining gene expression systems**

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The invention gene delivery system can also be used to deliver self-initiating and self-sustaining gene expression systems. Self-initiating and self-sustaining gene expression systems may be constructed by binding a RNA polymerase to a DNA construct *in vitro* prior to the introduction of the polynucleotide into the cell as described by Wagner *et al.* (U.S. Patent No. #5,591,601). The RNA polymerase is bound to a DNA construct containing a cognate promoter of the RNA polymerase operably linked to a DNA sequence encoding for the RNA polymerase.

20

The expression of functional RNA polymerase in turn enables the expression of any gene of interest that contains a cognate promoter sequence recognized by the same RNA polymerase in eukaryotic host cells. DNA sequences encoding for both RNA polymerase and gene product of interest (*i.e.*, protein of interest) may be contained within the same gene expression system. The gene expression system may be prebound to purified plasma lipoprotein fractions prior to transfection into eukaryotic cells.

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**g. Delivery of DNA to cells *in vivo***

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The invention gene delivery system can also be used to deliver DNA to cells *in vivo*. An expression vector containing the polynucleotide sequences of the gene of interest (*e.g.*, reporter gene or a healthy copy of a defective gene) is prebound to LDL according to the protocols described herein. This DNA-LDL complex is then introduced into an organism for example, a rat, mouse or human by, for example, intravenous injection. At varying times post-injection,

- 54 -

LDL is isolated from the blood and probed for DNA sequences of the type that were prebound to the LDL using standard molecular biological techniques such as, but not limited to, Southern blot hybridization or PCR™.

5       The LDL also can be immunoprecipitated with anti-LDL antibodies and then probed for specific DNA sequences bound to it. In order to determine cellular internalization and/or integration of the reporter gene sequences into the genomic DNA of cells of different tissues, total genomic DNA can be isolated from various tissues (according to standard molecular biology techniques) and probed for the presence of the reporter gene sequences using specific polynucleotide probes in PCR™ or Southern blot hybridization techniques. In addition, total 10 cellular RNA can be isolated from various different tissues using standard molecular biology techniques and probed for the presence of specific mRNA encoded for by the reporter gene polynucleotide sequences using specific antisense polynucleotide probes in Northern blot hybridization techniques or ribonuclease (RNase) protection assays.

15      Expression of a functional protein encoded for by the gene of interest in different tissues can be analyzed using techniques well known to the art, such as, Western blot hybridization of cellular protein extracts with antibodies that bind specifically to the reporter gene product (i.e., protein of interest) or direct detection of intracellular fluorescence (e.g., when reporter genes are 20 used that encode for blue or green fluorescent proteins (e.g., GFP from Clontech Inc.).

Several non-viral methods for the transfer of a DNA-LDL complex of the present invention into cultured mammalian cells also are contemplated by the present invention. These include calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 25 Rippe *et al.*, 1990) DEAE-dextran (Gopal, 1985), electroporation (Tur-Kaspa *et al.*, 1986; Potter *et al.*, 1984), direct microinjection (Harland and Weintraub, 1985), DNA-loaded liposomes (Nicolau and Sene, 1982; Fraley *et al.*, 1979) and lipofectamine-DNA complexes, cell sonication (Fechheimer *et al.*, 1987), gene bombardment using high velocity microprojectiles (Yang *et al.*, 1990), and receptor-mediated transfection (Wu and Wu, 1987; 30 Wu and Wu, 1988). Some of these techniques may be successfully adapted for *in vivo* or *ex vivo* use.

Once the DNA-LDL complex has been delivered into the cell, the nucleic acid encoding the gene of interest may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the gene may be stably integrated into the genome of the cell. This integration may be in the cognate location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the DNA-LDL complex is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of DNA molecule bound to the LDL.

In one embodiment of the invention, the DNA-LDL complex may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Neshif (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA-LDL complex into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

5 Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e.*, *ex vivo* treatment. Again, DNA encoding a particular gene may be delivered via this method and still be incorporated by the present invention.

10 In a further embodiment of the invention, the DNA-LDL complex may be entrapped in a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, 1991). Also contemplated are lipofectamine-DNA complexes.

15 20 Liposome-mediated nucleic acid delivery and expression of foreign DNA *in vitro* has been very successful. Wong *et al.* (1980) demonstrated the feasibility of liposome-mediated delivery and expression of foreign DNA in cultured chick embryo, HeLa and hepatoma cells. Nicolau *et al.* (1987) accomplished successful liposome-mediated gene transfer in rats after intravenous injection.

25 30 In certain embodiments of the invention, the liposome may be complexed with a hemagglutinating virus (HVJ). This has been shown to facilitate fusion with the cell membrane and promote cell entry of liposome-encapsulated DNA (Kaneda *et al.*, 1989). In other embodiments, the liposome may be complexed or employed in conjunction with nuclear non-histone chromosomal proteins (HMG-1) (Kato *et al.*, 1991). In yet further embodiments, the liposome may be complexed or employed in conjunction with both HVJ and HMG-1. In that such expression constructs have been successfully employed in transfer and expression of nucleic acid *in vitro* and *in vivo*, then they are applicable for the present invention. Where a bacterial promoter is employed in the DNA construct, it also will be desirable to include within the liposome an appropriate bacterial polymerase.

Other DNA-LDL complexes which can be employed to deliver a nucleic acid encoding a particular gene into cells are receptor-mediated delivery vehicles. These take advantage of the selective uptake of macromolecules by receptor-mediated endocytosis in almost all eukaryotic 5 cells. Because of the cell type-specific distribution of various receptors, the delivery can be highly specific (Wu and Wu, 1993).

Receptor-mediated gene targeting vehicles generally consist of two components: a cell receptor-specific ligand and a DNA-binding agent. Several ligands have been used for receptor-10 mediated gene transfer. The most extensively characterized ligands are asialoorosomucoid (ASOR) (Wu and Wu, 1987) and transferrin (Wagner *et al.*, 1990). Recently, a synthetic neoglycoprotein, which recognizes the same receptor as ASOR, has been used as a gene delivery vehicle (Ferkol *et al.*, 1993; Perales *et al.*, 1994) and epidermal growth factor (EGF) has also been used to deliver genes to squamous carcinoma cells (Myers, EPO 0273085).  
15

In other embodiments, the delivery vehicle may comprise a ligand and a liposome. For example, Nicolau *et al.*, (1987) employed lactosyl-ceramide, a galactose-terminal asialganglioside, incorporated into liposomes and observed an increase in the uptake of the insulin gene by hepatocytes. Thus, it is feasible that a nucleic acid encoding a particular gene 20 also may be specifically delivered into a cell type such as lung, epithelial or tumor cells, by any number of receptor-ligand systems with or without liposomes. For example, epidermal growth factor (EGF) may be used as the receptor for mediated delivery of a nucleic acid encoding a gene in many tumor cells that exhibit upregulation of EGF receptor. Mannose can be used to target the mannose receptor on liver cells. Also, antibodies to CD5 (CLL), CD22 (lymphoma), 25 CD25 (T-cell leukemia) and MAA (melanoma) can similarly be used as targeting moieties.

In certain embodiments, gene transfer may more easily be performed under *ex vivo* conditions. *Ex vivo* gene therapy refers to the isolation of cells from an animal, the delivery of a nucleic acid into the cells *in vitro*, and then the return of the modified cells back into an animal. 30 This may involve the surgical removal of tissue/organs from an animal or the primary culture of

cells and tissues. Anderson *et al.*, U.S. Patent 5,399,346, and incorporated herein in its entirety, disclose *ex vivo* therapeutic methods.

## 10. PHARMACEUTICAL

5 The gene delivery system of the instant invention can be administered *in vivo* in various ways including, but not limited to, intravenous, pharyngeal, epidermal, intramuscular, intraperitoneal (IP), nasal, and/or rectal. The gene delivery system of the instant invention can also be used for *in vitro* transfections of eukaryotic cell types which possess specific lipoprotein receptors on their cytoplasmic membranes, but is not limited to these cell types.

10

Pharmaceutical products that may spring from the current invention may comprise naked polynucleotide containing single or multiple copies of the specific nucleotide sequences that bind to specific DNA-binding sites of the apolipoproteins present on plasma lipoproteins as described in the current invention. The polynucleotide may encode a biologically active peptide, antisense RNA, or ribozyme and will be provided in a physiologically acceptable 15 administrable form.

15

Another pharmaceutical product that may spring from the current invention may comprise a highly purified plasma lipoprotein fraction, isolated according to the methodology, 20 described herein from either the patients blood or other source, and a polynucleotide containing single or multiple copies of the specific nucleotide sequences that bind to specific DNA-binding sites of the apolipoproteins present on plasma lipoproteins, prebound to the purified lipoprotein fraction in a physiologically acceptable, administrable form.

25

Yet another pharmaceutical product may comprise a highly purified plasma lipoprotein fraction which contains recombinant apolipoprotein fragments containing single or multiple copies of specific DNA-binding motifs, prebound to a polynucleotide containing single or multiple copies of the specific nucleotide sequences, in a physiologically acceptable 30 administrable form. Yet another pharmaceutical product may comprise a highly purified plasma lipoprotein fraction which contains recombinant apolipoprotein fragments containing single or multiple copies of specific DNA-binding motifs, prebound to a polynucleotide

- 59 -

containing single or multiple copies of the specific nucleotide sequences, in a physiologically acceptable administrable form.

5       The dosage to be administered depends to a great extent on the body weight and physical condition of the subject being treated as well as the route of administration and frequency of treatment. A pharmaceutical composition comprising the naked polynucleotide prebound to a highly purified lipoprotein fraction may be administered in amounts ranging from 1 µg to 1 mg polynucleotide and 1 µg to 100 mg protein.

10       Administration of the therapeutic virus particle to a patient will follow general protocols for the administration of chemotherapeutics, taking into account the toxicity, if any, of the vector. It is anticipated that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, as well as surgical intervention, may be applied in combination with the described gene therapy.

15       Where clinical application of a gene therapy is contemplated, it will be necessary to prepare the complex as a pharmaceutical composition appropriate for the intended application. Generally this will entail preparing a pharmaceutical composition that is essentially free of pyrogens, as well as any other impurities that could be harmful to humans or animals. One also will generally desire to employ appropriate salts and buffers to render the complex stable and allow for complex uptake by target cells.

20       Aqueous compositions of the present invention comprise an effective amount of the compound, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. Such compositions can also be referred to as inocula. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is

- 60 -

incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The compositions of the present invention may include classic pharmaceutical preparations. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

5           *i) Disease States*

10          A wide variety of disease states may be treated with compositions according to the present invention. In essence, any disease that can be treated by provision of a protein or nucleic acid is amenable to this approach. Disease states include a variety of genetic abnormalities such as diabetes, cancer, cystic fibrosis and various other diseases that could be treated by increasing or decreasing expression of a protein in a target cell.

15          Depending on the particular disease to be treated, administration of therapeutic compositions according to the present invention will be via any common route so long as the target tissue is available via that route. This includes oral, nasal, buccal, rectal, vaginal or topical. Topical administration would be particularly advantageous for treatment of skin cancers. Alternatively, administration will be by orthotopic, intradermal, subcutaneous, 20 intramuscular, intraperitoneal or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions that include physiologically acceptable carriers, buffers or other excipients.

25          In certain embodiments, *ex vivo* therapies also are contemplated. *Ex vivo* therapies involve the removal, from a patient, of target cells. The cells are treated outside the patient's body and then returned. One example of *ex vivo* therapy would involve a variation of autologous bone marrow transplant. Many times, ABMT fails because some cancer cells are present in the withdrawn bone marrow, and return of the bone marrow to the treated patient results in repopulation of the patient with cancer cells. In one embodiment, however, the 30 withdrawn bone marrow cells could be treated while outside the patient with an LDL-DNA

- 61 -

particle that targets and kills the cancer cell. Once the bone marrow cells are "purged," they can be reintroduced into the patient.

The treatments may include various "unit doses." Unit dose is defined as containing a predetermined-quantity of the therapeutic composition calculated to produce the desired responses in association with its administration, *i.e.*, the appropriate route and treatment regimen. The quantity to be administered, and the particular route and formulation, are within the skill of those in the clinical arts. Also of import is the subject to be treated, in particular, the state of the subject and the protection desired. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time. Unit dose of the present invention may conveniently be described in terms of 0.01mg DNA/kg body weight to 0.4mg DNA/kg body weight, with ranges in between these being contemplated such that 0.05, 0.10, 0.15, 0.20, 0.25, 0.5mg/DNA/kg body weight are administered. Likewise the amount of LDL delivered can vary from about 0.2 to about 8.0 mg/kg body weight. Thus in particular embodiments, 0.4 mg, 0.5 mg, 0.8 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 4.0 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg and 7.5 mg of LDL may be delivered to an individual *in vivo*. The dosage of DNA:LDL to be administered depends to a great extent on the weight and physical condition of the subject being treated as well as the route of administration and the frequency of treatment. A pharmaceutical composition comprising the naked polynucleotide prebound to a highly purified lipoprotein fraction may be administered in amounts ranging from 1  $\mu$ g to 1mg polynucleotide to 1 $\mu$ g to 100mg protein. Thus, particular compositions may comprise 1 $\mu$ g, 5 $\mu$ g, 10 $\mu$ g, 20 $\mu$ g, 30 $\mu$ g, 40 $\mu$ g, 50 $\mu$ g, 60 $\mu$ g, 70 $\mu$ g, 80 $\mu$ g, 100 $\mu$ g, 150 $\mu$ g, 200 $\mu$ g, 250 $\mu$ g, 500 $\mu$ g, 600 $\mu$ g, 700 $\mu$ g, 800 $\mu$ g, 900 $\mu$ g or 1000 $\mu$ g polynucleotide that is bound independently to 1 $\mu$ g, 5 $\mu$ g, 10 $\mu$ g, 20 $\mu$ g, 3.0 $\mu$ g, 40 $\mu$ g, 50 $\mu$ g, 60 $\mu$ g, 70 $\mu$ g, 80 $\mu$ g, 100 $\mu$ g, 150 $\mu$ g, 200 $\mu$ g, 250 $\mu$ g, 500 $\mu$ g, 600 $\mu$ g, 700 $\mu$ g, 800 $\mu$ g, 900 $\mu$ g or 1000 $\mu$ g, 1.5mg, 5 mg, 10 mg, 20mg, 30mg, 40mg, 50mg, 60 mg, 70mg, 80 mg, 90 mg or 100mg lipoprotein. Any amount of polynucleotide may be bound to any other amount of lipoprotein to achieve the pharmaceutical concentrations of the present invention.

**ii) Cancer**

One of the preferred embodiments of the present invention involves the use of the LDL vectors to deliver therapeutic genes to cancer cells. Target cancer cells include cancers of the lung, brain, prostate, kidney, liver, ovary, breast, skin, stomach, esophagus, head & neck, testicles, colon, cervix, lymphatic system and blood. Of particular interest are non-small cell lung carcinomas including squamous cell carcinomas, adenocarcinomas and large cell undifferentiated carcinomas.

According to the present invention, one may treat the cancer by directly injection a tumor with the LDL vector. Alternatively, the tumor may be infused or perfused with the vector using any suitable delivery vehicle. Local or regional administration, with respect to the tumor, also is contemplated. Finally, systemic administration may be performed. Continuous administration also may be applied where appropriate, for example, where a tumor is excised and the tumor bed is treated to eliminate residual, microscopic disease. Delivery via syringe or catheterization is preferred. Such continuous perfusion may take place for a period from about 1-2 hours, to about 2-6 hours, to about 6-12 hours, to about 12-24 hours, to about 1-2 days, to about 1-2 weeks or longer following the initiation of treatment. Generally, the dose of the therapeutic composition via continuous perfusion will be equivalent to that given by a single or multiple injections, adjusted over a period of time during which the perfusion occurs.

For tumors of  $\geq 4$  cm, the volume to be administered will be about 4-10 ml (preferably 10 ml), while for tumors of  $< 4$  cm, a volume of about 1-3 ml will be used (preferably 3 ml). Multiple injections delivered as single dose comprise about 0.1 to about 0.5 ml volumes. The LDL-DNA particles may advantageously be contacted by administering multiple injections to the tumor, spaced at approximately 1 cm intervals.

In certain embodiments, the tumor being treated may not, at least initially, be resectable. Treatments with therapeutic constructs may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site.

- 63 -

5 A typical course of treatment, for a primary tumor or a post-excision tumor bed, will involve multiple doses. Typical primary tumor treatment involves a 6 dose application over a two week period. The two week regimen may be repeated one, two, three, four, five, six or more times. During a course of treatment, the need to complete the planned dosings may be reevaluated.

10 Cancer therapies also include a variety of combination therapies with both chemical and radiation based treatments. Combination chemotherapies include, for example, cisplatin (CDDP), carboplatin, procarbazine, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxol, transplatinum, 5-fluorouracil, vincristin, vinblastin and methotrexate.

15 Combination radiation therapies may be x- and  $\gamma$ -irradiation. Dosage ranges for x-irradiation range from daily doses of 2000 to 6000 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosages for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by neoplastic cells.

20

Various combinations may be employed, gene therapy is "A" and the radio- or chemotherapeutic agent is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B

25

B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

30

The terms "contacted" and "exposed," when applied to a cell, are used herein to describe the process by which a therapeutic construct and a chemotherapeutic or radiotherapeutic agent

- 64 -

are delivered to a target cell or are placed in direct juxtaposition with the target cell. To achieve cell killing or stasis, both agents are delivered to a cell in a combined amount effective to kill the cell or prevent it from dividing.

5       The therapeutic compositions of the present invention are advantageously administered in the form of injectable compositions either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. These preparations also may be emulsified. A typical composition for such purpose comprises a pharmaceutically acceptable carrier. For instance, the composition may contain 10 mg, 25 mg,  
10 50 mg or up to about 100 mg of human serum albumin per milliliter of phosphate buffered saline.

15      Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oil and injectable organic esters such as ethyloleate. Aqueous carriers include water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles such as sodium chloride, Ringer's dextrose, etc. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial agents, anti-oxidants, chelating agents and inert gases. The pH and exact concentration of the various  
20 components the pharmaceutical composition are adjusted according to well known parameters.

25      Additional formulations are suitable for oral administration. Oral formulations include such typical excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. The compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders. When the route is topical, the form may be a cream, ointment, salve or spray.

## 11. EXAMPLES

30      The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in

- 65 -

the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

5

## EXAMPLE 1

### MATERIALS AND METHODS

#### 1. Isolation of Plasma Lipoproteins

10        Restriction endonucleases were purchased from Life Technologies, and Protease inhibitors (*i.e.*, leupeptin, PMSF, and Trasylol) were purchased from Sigma Chemical Company. Plasma lipoproteins were isolated using standard sequential flotation ultracentrifugation methods as described (Schumaker and Puppione, 1986). Throughout the entire procedure samples were kept on ice or at 4°C unless otherwise stated.

15

Subjects were fasted for at least 4 h prior to the start of the experimental procedures. Blood was drawn into sterile, vacuumed glass tubes containing anticoagulants, *e.g.*, 0.1% (ethylenedinitrolo)-tetracetic acid (EDTA) or heparin. Plasma was obtained by centrifugation (10 minutes at 3000 × g) and immediately adjusted to 0.005% phenylmethylsulfonyl fluoride (PMSF), 10KIU Trasylol/ml, and 1 µg leupeptin/ml. VLDL, LDL, and HDL fractions were isolated by sequential flotation ultracentrifugation for 18 h at 40,000 rpm in a Beckmann centrifuge Model LS-80M after plasma samples were adjusted with potassium bromide (ICBr) to solution densities of 1.006, 1.019, and 1.215 g/ml respectively. Immediately following ultracentrifugation, individual lipoprotein fractions were collected and dialyzed extensively against phosphate buffered saline (pH 7.4) containing 0.001% sodium azide. Protein concentrations were determined using standard BCA protein assays (Pierce Chemical Company).

20

25

#### 2. Dna-Binding Protocol

30        Lipoproteins and DNA were mixed together and incubated for 30 min at room temperature in 50 mmole/liter Tris (pH 7.4), 100-154 mmoles/liter sodium chloride (NaCl), 15

- 66 -

5 mmoles/liter magnesium chloride ( $MgCl_2$ ). 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) was added to the samples in a 1:5 V/V ratio. Samples were underloaded into 30  $\mu$ l wells at the cathode edge of an 0.8% agarose gel containing 1  $\mu$ g ethidium bromide/ml in Tris-Acetate buffer (pH 7.85) and electrophoresis was accomplished using 100 Volt constant until the negatively charged tracking dye had migrated at least 50% of distance from the loading well to the anodic edge of the gel.

### 3. Agarose Electrophoretogram of Human Lipoproteins

10 Agarose electrophoresis of human lipoproteins has been performed to illustrating the differential migration patterns of lipoprotein fractions VLDL, LDL, and HDL isolated from human plasma resolved using non-denaturing conditions.

15 Plasma lipoproteins were isolated from human blood according to the protocol described above. 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) was added to the samples in a 1:5 V/V ratio. Samples were underloaded into 30  $\mu$ l wells at the cathode edge of an 0.8% agarose gel in Tris-Acetate buffer (pH 7.85) and electrophoresis was accomplished using 100 Volt constant until the negatively charged tracking dye had migrated at least 50% of the distance from the loading well to the anodic edge of the gel.

20 Following electrophoresis, the agarose gel was stained for protein in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomasie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). Lane 1 contained human VLDL (10  $\mu$ g protein), Lane 2 contained human LDL (35  $\mu$ g protein), and Lane 3 contained human HDL (35  $\mu$ g protein).  
25 Results illustrated the differential migration of lipoprotein fractions, VLDL, LDL, and HDL, isolated from human plasma resolved using non-denaturing conditions by agarose gel electrophoresis. Lipoproteins were visualized using a protein binding dye, Coomassie Brilliant Blue (CBB). The absence of other bands in each lane indicated the high degree of purity for each lipoprotein.

30

4. Radioisotope Labeling of Deoxyoligonucleotides

Complementary single stranded oligonucleotides were mixed (10 µg each) and incubated at 85°C for 5 min in 10 mM Tris HCl (pH 7.4). Immediately following incubation, the samples were cooled down slowly to room temperature to obtain double stranded oligonucleotides. The double stranded oligonucleotides were then digested with *Bam*HI and *Eco*RI for 1 h at 37°C in 50 mM Tris HCl (pH 8.0), 100 mM NAG1, and 10 mM MgCl<sub>2</sub>. Digested double stranded oligonucleotides were purified using a Qiaquick nucleotide removal kit from Qiagen Inc. according to manufacturer's protocol. The 5' protruding ends of the purified oligonucleotides were then labeled with <sup>32</sup>P-αdATP using a Prime-It II labeling kit containing Exo (-) Klenow enzyme from Stratagene Inc. according to the manufacturer's protocol. The specific activity of all oligonucleotides was determined by scintillation counting.

The DNA-binding studies were performed as described above except that the agarose gel was not stained with ethidium bromide. Instead, following electrophoresis, the agarose gel was dried under vacuum and exposed to X-ray film for 4 h at room temperature prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (Bio-Rad Labs). Oligonucleotides and human LDL were present at 400,000 cpm and 40 µg protein per lane respectively.

20 5. Sonication of plasma lipoproteins

Solutions of plasma lipoproteins in phosphate-buffered saline containing 10 mM MgCl<sub>2</sub> were kept on ice and sonicated for various time periods ranging from 0 to 6 minutes in a Sonifier Model 350 sonicator (Branson Sonic Power Co.) at the following settings: duty cycle; 30%, pulsed, output control; level 2. Immediately following sonication, genomic DNA was added to the sonicated solutions, and the DNA-binding assay (see above) was started.

25 6. RT-PCR™ of Lipoprotein-bound RNA

Human liver RNA, complexed to human LDL or to human VLDL as described above, was subjected to agarose gel electrophoresis and extracted from the gel by solubilizing the gel for 20 min at 50°C in 3 times the gel volume of QX-1 buffer (Qiagen) and by twice adding an equivalent volume of phenol/chloroform (pH 4.0). RNA was precipitated by adding an

- 68 -

equivalent volume of 100% isopropanol and freezing the mixture overnight at -80°C. RNA pellets were dissolved in 50 µl of DEPC-treated water. For each reaction, the dissolved RNA (3 µl) was transcribed in reverse into single-stranded DNA by adding 100 mM KCl, 10 mM Tris-HCl (pH 8.3), 5 mM MgCl<sub>2</sub>, 2.5 µM primer (oligo d(T) or random hexamers), 1 U/µl RNase inhibitor, 1 mM each of dATP, dCTP, dTTP, and dGTP, and 2.5 U/µl of MuLV reverse transcriptase in a total reaction volume of 20 µl. The single-stranded DNA samples were then amplified in 100 mM KCl, 10 mM Tris-HCl (pH 8.3), 2 mM MgCl<sub>2</sub>, 0.15 µM each of the forward and reverse ISRE primers (see Table 2), 1 mM each of dATP, dCTP, dTTP, and dGTP, and 2.5 U/100 µl of AmpliTaq DNA polymerase in a total reaction volume of 100 µl. DNA amplification was carried out in a thermocycler in 30 consecutive cycles of denaturing at 95°C for 60 sec, reannealing at 55°C for 60 sec, primer extension at 72°C for 120 sec, and a final extension at 72°C for 7 min. For each PCR reaction, 10 µl of the reaction mixture was analyzed by electrophoresis on a 1% agarose gel in TBE buffer (45 mM Tris-borate and 1 mM EDTA, pH 8.0) while maintaining a 100-V constant for 1 h. The PCR products were visualized by staining the gel with ethidium bromide.

#### 7. DNA sequencing

DNA fragments obtained from the RT-PCR reactions were separated by electrophoresis on a 1% agarose gel and extracted from the gel by using a Qiagen gel extraction kit according to the manufacturer's protocol. DNA samples were analyzed on an Applied Biosystems Inc. model 373 automated DNA sequence apparatus after dye-terminator thermo cycle sequencing.

#### 8. Cell culture and transfection assays.

Human skin fibroblasts were cultured in complete growth medium consisting of Dulbecco's modified Eagle's medium that was supplemented with 10% fetal bovine serum, 100 µg/ml each of streptomycin and penicillin at 37°C in an atmosphere of 5% CO<sub>2</sub> in a humidified incubator. Twenty-four hours before cell transfection, during exponential growth, the cultured cells were harvested by trypsinization, replated at a cell density of 1 × 10<sup>6</sup> cells in 35-mm culture dishes containing a glass coverslip, and cultured in complete growth medium. All transfection experiments were performed in triplicate as described.

**9. LipoFectin assay.**

The pEGFP-N1 plasmid and LipoFectin were mixed together at a ratio of 1:4 (wt/wt) in 200 µl of serum-free medium and incubated for 15 min at room temperature. When the cells reached 40 to 60% confluence, they were transfected with a mixture of 5 µg of DNA and 20 µg of LipoFectin per 35-mm culture dish, each dish having been diluted in 1 ml of serum-free medium. Transfection was performed for 16 h at 37°C. Once transfection was achieved, the liposomes were removed from the culture dish by gentle washing and maintained in 2 ml of growth medium per 35-mm culture dish for 24 h at 37°C. Expression of GFP in the cells was determined by fluorescence microscopy

10

**10. LDL assay.**

The pEGFP-N1 plasmid and LDL were mixed together at a ratio of 1:10 (wt/wt) in 100 µl of serum-free medium containing 10 mM MgCl<sub>2</sub> and incubated for 15 min at 37°C. When the cells were 40 to 60% confluent, they were transfected for 16 h at 37°C with a mixture of 5 µg of DNA and 50 µg of LDL per 35-mm culture dish, each dish having been diluted in 1 ml of serum-free medium. Once transfection was achieved, the LDLs were removed by gentle washing and maintained in 2 ml of growth medium per 35-mm culture dish for 24 h at 37°C. At 24 h after transfection, the cells were washed with PBS and fixed in 2 ml of PBS containing 4% paraformaldehyde per 35-mm culture dish for 30 min. The coverslips were then removed from the culture dishes, washed with PBS, placed in an inverted orientation on glass slides, and examined by fluorescent microscopy to detect GFP.

**11. *In vivo* reporter gene expression.**

Two-month-old female Sprague-Dawley rats were anesthetized with a combination anesthetic (42.8 mg/ml ketamine, 8.6 mg/ml xylazine, and 1.4 mg/ml acepromazine), and a prebound complex of purified rat LDL and linearized pEGFP-N1 plasmid DNA was injected intravenously (into the femoral vein), subcutaneously, intraperitoneally, and into the pharyngeal, nasal, and rectal mucosae (100 µg of LDL protein and 5 µg of DNA in 100 µl of PBS containing 10 mM MgCl<sub>2</sub> per site). Control animals were injected with linearized pEGFP-N1 plasmid DNA in which the HCMV IE promoter sequence was interrupted only by digestion with restriction enzymes. 5 µg of DNA in 100 µl of PBS containing 10 mM MgCl<sub>2</sub> per site.

- 70 -

After 2, 5, or 7 days, all the treated and control rats were sacrificed, their blood was collected by means of cardiac puncture, and the tissues were excised and immobilized in OCT by means of snap freezing over liquid nitrogen or by immediate freezing in liquid nitrogen. The immobilized tissue samples were sectioned on a cryomicrotome, and the sections (5–8 µm thick) were fixed for 30 min in 4% paraformaldehyde and analyzed for expression of EGFP (green fluorescent protein) by fluorescent microscopy.

#### 12. Fluorescent microscopy.

Microscopy was performed by using an Olympus Model BH-2 fluorescent microscope (Olympus, USA) equipped with a digital camera (Hamamatsu, Model C5810) and a color printer (Image Master, Toshiba). The filter set used was a standard fluorescein isothiocyanate (FITC) set (Chroma Technology, Brattleboro, VT, USA). The maximum excitation and emission wavelengths for this filter set were 485 nm (range 460–510 nm) and 540 nm (range 515–565 nm), respectively. Transfection efficiency was determined by calculating the average percentage of transduced cells of five different fields per 35-mm culture dish.

#### 13. Detection of GFP.

Excised rat tissues were homogenized in 150 µl of PBS in a dounce homogenizer placed on ice. The homogenized tissues were centrifuged for 3 min at 13,000 × g, and 50-µl aliquots were withdrawn and used in an ELISA assay to detect GFP. First, serial dilutions (range 1:10 to 1:1,000) of all samples were made in PBS. ELISA plates (96 wells) were coated with the samples (three wells/sample) by incubating the plates at room temperature for 3 h. The plated samples were then washed three times with 200 µl of 1 × PBS containing 0.1% Tween 20 (PBST) and blocked with 200 µl of PBST containing 1% bovine serum albumin (BSA) for 2 h at room temperature while shaking gently. The washing procedure was repeated with 200 µl of PBST containing 0.1% BSA, and the plated samples were incubated with a 1:2,000 dilution of a recombinant GFP polyclonal antibody (IgG fraction, Clontech Inc., Palo Alto, CA) in PBST containing 0.1% BSA (50 µl of diluted mixture per well) for 18 h at 4°C while shaking gently. The plated samples were washed and incubated with a 1:5000 dilution of HRP-conjugated goat anti-rabbit antibody (IgG fraction, Cappel, Durham, NC) in PBST containing 0.1% BSA for 1 h at room temperature while shaking gently. The washing procedure was repeated and was

- 71 -

followed by a final wash with 1 × PBS. GFP was detected after a 30-min incubation at room temperature in PBS containing σ-phenylenediamine as a chromogenic substrate.

## EXAMPLE 2

### BINDING OF HUMAN GENOMIC DNA TO HUMAN LDL

5       The binding of human genomic DNA (hg DNA) to human LDL has also been demonstrated. Each lane of the agarose gel contained hg DNA cut with *AluI* or *HindIII*. In addition, human VLDL and mouse LDL were run alongside the hg DNA.

10      Plasma lipoproteins were isolated from human or mouse blood according to the protocol described above. DNA-binding studies were performed using human genomic DNA digested with either *AluI* or *HindIII*. Following electrophoresis, the gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomasie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs).

15      Each lane contained 5 µg human genomic DNA (hg DNA) cut with *AluI* or *HindIII*. In addition, human VLDL (10 µg protein per lane) human LDL (35 µg protein per lane) and mouse LDL (10 µg protein per lane) were also analysed.

20      Bands in this study showed specific binding of digested human DNA fragments and human LDL by gel-shift electrophoresis. DNA fragment obtained by *AluI* or *HindIII* digestion of human genomic DNA are shown to migrate toward the anode with much slower mobility when preincubated with human LDL but not when incubated with human VLDL, human HDL, or mouse LDL. The complexed DNA/lipoprotein band are first visualized using DNA-binding ethidium bromide and photographed using transmitted ultra-violet light for activation of the fluorescent dye. Lipoproteins were next visualized with CBB and photographed using transmitted visible light. The results shown in this figure indicate that aliquots of *AluI*- and *Hind III*-digested human genomic DNA fragments comigrate with human LDL and are therefore bound to human LDL.

25      While *AluI*, and *HindIII* were used to digest genomic DNA in the studies shown here, the inventors of the instant invention have also used *BamHI*, and *PvuII* for genomic DNA digest.

- 72 -

It is understood by those of skill in the art that there are many known restriction enzymes. All of which are capable of genomic DNA digestion resulting in DNA that can be successfully bound to LDL. DNA digested with *Alu*I yields DNA of very small size (200-700 nucleotides) which allows isolation of the slower migrating digested DNA bound to LDL from the unbound 5 digested DNA using agarose gel electrophoresis. Digestion of genomic DNA with *Hind*III yields genomic DNA of greater average size (1000-7000 nucleotides) which reaches the upper size limit for separation by agarose gel electrophoresis (the technique used here), however there are other known DNA separation techniques which would work similarly to accomplish the goal of separating free DNA from DNA bound to LDL. The choice of which separation 10 technique to use is dependent only on the size of the DNA fragments resulting after digestion. In principal, undigested genomic DNA would also work.

### EXAMPLE 3 BINDING OF PLASMID DNA TO HUMAN LDL

15 Plasma LDL were isolated from human blood according to the protocol previously described in Example 1. DNA-binding studies were using DNA (pBluescript II KS, Stratagene Inc.) digested with *Pvu* I. Following electrophoresis, the agarose gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). The 20 binding of plasmid DNA to human LDL was shown in a gel which contained 0.5 µg molecular size DNA marker (Lane 1); 2 µg pKS DNA cut with *Pvu* I (Lanes 2-4); 35 µg human LDL (Lane 3) and 70 µg human LDL protein (Lane 4).

25 Results of the electrophoretogram illustrated specific binding of *Pvu*I digested plasmid DNA (pBluescript II KS, Stratagene Inc.) and human LDL. Increased amounts of human LDL also caused an increase of DNA shifted to the LDL location and a decrease of the free *Pvu* I digested DNA band. Co-migration of the *Pvu* I digested DNA and human LDL are proof of a physical complex composed of LDL and DNA.

- 73 -

**EXAMPLE 4**  
**BINDING OF CMV PROMOTER-REGULATORY**  
**SEQUENCES TO HUMAN LDL**

Plasma lipoproteins were isolated from human or mouse blood according to the protocol  
5 previously described in Example 1. DNA-binding studies were performed using plasmid DNA  
(either pBluescript II KS or pBKCMV, Stratagene Inc.) digested with *Bam*HI. Following  
electrophoresis the agarose gel was stained for DNA with ethidium bromide prior to protein  
staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie  
Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). Loading quantities per lane were as follows:

10	plasmid DNA:	1 µg DNA/lane
	human VLDL	35 µg protein/lane
	human LDL	35 µg protein/lane
	mouse VLDL:	8 µg protein/lane
	mouse LDL:	35 µg protein/lane

15 This study used *Bam*HI cut pIGS, *Bam*HI cut pBKCMV, human VLDL, human LDL, mouse  
VLDL and mouse LDL.

A comparison of human LDL complexed with *Bam*HI linearized plasmids, pBluescript  
II KS or pBKCMV. The inventors' results illustrated that specific binding of *Bam*HI linearized  
20 plasmid DNA and human LDL occurs, but these *Bam*HI linearized plasmids do not complex  
with either human VLDL, mouse VLDL or mouse LDL under the conditions previously  
described in the DNA-binding protocol (Example 2). Further, enhanced binding of human LDL  
and the *Bam*HI linearized plasmid pBKCMV DNA which contains the cytomegalovirus  
25 promoter region SEQ ID NO:225 (Table 2) was observed as compared to the *Bam*HI linearized  
plasmid pBluescript II KS DNA that does not contain the cytomegalovirus promoter region  
(lane 3). Because binding of DNA by LDL is enhanced in the presence of the CMV promoter,  
it is possible that LDL binds specifically to the CMV promoter sequence (SEQ ID NO:225, see  
Table 2).

30 Aliquots containing approximately 8 µg mouse VLDL protein were used in each DNA-  
binding assay mixtures resolved in lanes 4 and 9 as compared to 35 µg of total protein of all

- 74 -

other lipoproteins (lanes 2, 3, 5, 7, 8, and 10). Due to the low physiological concentration of VLDL in mouse plasma and the limited loading capacity of the gel, it was not possible to load 35 µg of mouse VLDL protein per lane. Therefore, this study does not allow for a quantitative comparison of the plasmid DNA-binding capacity of mouse VLDL vs. human VLDL, human LDL, and mouse LDL.

**TABLE 2**  
**Nucleotide Sequence of the Promoter Region (1300-1900) of the Human Cytomegalovirus**  
**SEQ ID NO:225**

GGATCTGACG	GTTCACTAAA	CCAGCTCTGC	TTATATAGAC	CTCCCACCGT
ACACGCCTAC	<u>CGCCCATTG</u>	<u>CGTCAATGGG</u>	<u>GCGGAGTTGT</u>	TACGACATTT
TGGAAAGTCC	CGTTGATTTC	GGTGCCAAAA	<u>CAAACCTCCAT</u>	<u>TGACGTCAAT</u>
<u>GGGGTGGAGA</u>	CTTGGAAATC	CCCGTGAGTC	AAACCGCTAT	CCACGCCCAT
<u>TGATGTACTG</u>	<u>CCAAAACCGC</u>	ATCACCATGG	TAATAGCGAT	GACTAATAACG
<u>TAGATGTACT</u>	<u>GCCAAGTAGG</u>	AAAGTCCCAT	AAGGTCATGT	ACTGGGCATA
ATGCCAGGCG	<u>GGCCATTTAC</u>	<u>CGTCATTGAC</u>	<u>GTCAATAGGG</u>	<u>GGCGTACTTG</u>
GCATATGATA	CACTTGATGT	ACTGCCAAGT	GGGCAGTTA	CCGTAATAAC
TCCACCCATT	GACGTCAATG	GAAAGTCCCT	ATTGGCGTTA	CTATGGGAAC
<u>ATACGTCAATT</u>	<u>ATTGACGTCA</u>	<u>ATGGGCGGGG</u>	<u>GTCGTTGGGC</u>	GGTCAGCCAG
<u>GCGGGCCATT</u>	<u>TACCGTAAGT</u>	TATGTAACGC	GGAACTCCAT	ATATGGGCTA
TGAACTAATG	<u>ACCCCGTAAT</u>	TGATTACTAT	TAATAACTA	

10

Major repeat regions are indicate in bold and underlined.

- 75 -

**EXAMPLE 5**  
**BINDING OF SRE, E/C, FAS, AND ISRE**  
**DEOXYNUCLEOTIDE SEQUENCES TO HUMAN LDL**

Plasma lipoproteins were isolated from human or mouse blood according to the protocol  
5 previously described in Example 1. DNA-binding studies were performed using the synthetic oligonucleotides: SRE, E/C, and FAS (see Table 3 for nucleotide sequences).

**TABLE 3**  
**Deoxyribonucleic Acid Sequences of Synthetic Oligonucleotides**  
10                   **used in Binding Studies with LDL**

SEQ ID NO	Oligo Name	Sequence (5'-3')
226	SRE-2A	GATCCAAATCACCCACTGCAACTCCTCCCCCTGCG
227	E/C-1A	GATCCATCCAATTGGGCAATCAGGAG
228	FAS- 1A	GATCCGGTCTCCAATTGG
229	ISRE- 1A	GATCCTCGGGAAAGGGAAACCGAAACTGAAGCCG

DNA-binding studies were performed according to the previously described DNA-binding protocol (Example 2). Following electrophoresis, the agarose gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 1096 V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs).  
15 Oligonucleotides were present at 1 µg DNA per lane. Lanes containing human LDL contained 35 µg protein per lane and lanes containing mouse LDL contained 15 µg protein per lane.

The data generated showed the complexed synthetic, double-stranded oligonucleotide fragments and human LDL. The results strongly support that human LDL binds to these DNA sequences in a highly specific fashion. The synthetic oligonucleotides SRE-2A, E/C-1A, FAS-1A, and ISRE-1A (Table 3, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229 respectively) bind to human LDL but do not bind to mouse LDL. DNA binding to human LDL is illustrated by the appearance of a fraction of slower mobility DNA that comigrates with human LDL.  
20  
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In another embodiment of this same study, binding was determined using radioisotope labeling of the deoxynucleotide sequences as described in Example 1. The results from these DNA-binding studies show that human LDL binds to the synthetic oligonucleotides SRE-2A, 5 E/C-IA, FAS-IA, and ISRE-IA (Table 3, SEQ ID NO:226; SEQ ID NO:227; SEQ ID NO:228; SEQ ID NO:229) in a highly specific fashion. DNA binding to human LDL is illustrated by the appearance of a fraction of slower mobility DNA that comigrates with human LDL. The binding affinity of the different synthetic oligonucleotides for human LDL can be determined by kinetic binding studies using quantitative autoradiography well known to those of skill in the 10 art.

#### EXAMPLE 6

#### BINDING OF VARIOUS NUCLEOTIDE SEQUENCES TO THE LDL ISOLATED FROM VARIOUS SPECIES

15 Plasma lipoproteins were isolated from human, mouse, rat, or baboon blood according to the protocol previously described in Example 1. DNA-binding studies were performed according to the previously described DNA-binding protocol using the synthetic oligonucleotides: SRE, E/C, and FAS (see Table 3 for nucleotide sequences), genomic DNA, or plasmid DNA containing the CMV promoter. A summary of the binding studies of the instant invention are illustrated in Tables 4A and 4B, below. Table 4A illustrates the binding of 20 human, mouse, rat and baboon LDL to various forms and sources of DNA, and Table 4B illustrates the DNA/LDL complexes made thus far.

25 TABLE 4A  
**Binding of Human, Mouse, Rat and Baboon LDL to Various Forms of DNA**

DNA	human LDL	mouse LDL	rat LDL	baboon LDL
hg DNA	YES	NO	YES	YES
mg DNA	N.D.	N.D.	YES	N.D.

- 77 -

rg DNA	N.D.	N.D.	YES	N.D.
bg DNA	N.D.	N.D.	N.D.	YES
CMV	YES	NO	YES	YES
SRE	YES	NO	N.D.	NO
E/C	YES	NO	N.D.	NO
FAS	YES	NO	N.D.	NO

hg = human genomic DNA (digested with either *AluI* or *HindIII*, mg = mouse genomic DNA digested with either *AluI* or *HindIII*, rg = rat genomic DNA digested with either *AluI* or *HindIII*. and bg = baboon genomic DNA digested with either *AluI* or *HindIII*

Yes = binding, NO = no binding, N.D. = binding not determined

- 78 -

**TABLE 4B**  
**Specific LDL/DNA Complexes That Have Been Made**

DNA	DNA Digested With	LDL
human genomic	<i>AluI</i>	human
human genomic	<i>HindIII</i>	human
human genomic	<i>Bam HI</i>	human
human genomic	<i>Pvu I</i>	human
human genomic	<i>AluI</i>	rat
human genomic	<i>HindIII</i>	rat
human genomic	<i>Bam HI</i>	rat
human genomic	<i>Pvu I</i>	rat
human genomic	<i>AluI</i>	baboon
human genomic	<i>HindIII</i>	baboon
human genomic	<i>Bam HI</i>	baboon
human genomic	<i>Pvu I</i>	baboon
mouse genomic	<i>AluI</i>	rat
mouse genomic	<i>HindIII</i>	rat
rat genomic	<i>AluI</i>	rat
rat genomic	<i>HindIII</i>	rat
baboon genomic	<i>AluI</i>	baboon
baboon genomic	<i>HindIII</i>	baboon
pBSKS	<i>Pvu I</i>	human
pBSKS	<i>Bam HI</i>	human
pBKCMV	<i>Bam HI</i>	human
pBKCMV	<i>Bam HI</i>	rat

- 79 -

TABLE 4B (cont'd)

DNA	DNA Digested With	LDL
pBKCMV	<i>Bam</i> HI	baboon
SRE-2A oligo	none	human
SEQ ID NO:226		
E/C-1A oligo	none	human
SEQ ID NO:227		
FAS-1A oligo	none	human
SEQ ID NO:228		
ISRE-1A oligo	none	human
SEQ ID NO:229		

**EXAMPLE 7****DETECTION OF LDL-BOUND DNA IN HUMAN BLOOD**

5 Plasma lipoproteins are isolated from human blood according to the protocol previously described in Example 1. 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) is added to the samples in a 1:5 V/V ratio. Samples are underloaded into 30 µl wells at the cathode edge of an 0.8% agarose gel in Tris-Acetate buffer (pH 7.85) and electrophoresis is accomplished using 100 Volt constant until the negatively charged tracking dye migrates at least 50% of the distance from the loading well to the anodic edge of the gel.

10 Following electrophoresis, is stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic add, and 0.25% Coomasie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). If no DNA is detected by ethidium bromide staining, the agarose gel is subjected to Southern blot analysis using a labeled DNA probe. The DNA is labeled with a radioactive isotope (e.g.,  $^{32}\text{P}$ ), a non-radioactive tag (DIG) or with any other standard DNA-labeling method known to one of skill in the art. Randomly synthesized, short oligonucleotides are used as the probe to detect, in a general fashion, whether or not DNA is bound to the isolated LDL. Controls include lanes containing known quantities of DNA, lanes

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- 80 -

containing purified LDL digested with DNase I, and LDL bound to DNA made by mixing purified LDL and DNA according to the method described in Example 2.

5       LDL isolated from humans with cancer and subjected to the above protocol will have detectable DNA bound to the LDL in quantities greater than the amount of DNA bound to LDL isolated from humans without cancer.

**EXAMPLE 8**  
**DETECTION OF SPECIFIC TYPES OF CANCERS WITH**  
**SEQUENCE SPECIFIC DNA PROBES**

10      Not only is it possible to identify the presence or absence of cancer in a living body using the invention technique (as described in Example 14 above), it is also possible to identify specific cancer types by using sequence specific DNA probes. For example, LDL-bound DNA isolated from a patient with colon cancer will have a different DNA sequence than the LDL-bound DNA isolated from a patient with a different cancer type, for example, breast cancer.  
15      Different DNA sequences bound to the LDL isolated from different cancer patients is determined by first isolating LDL from the blood of a person with an independently identified and known cancer type, using the protocol in Example 1. This isolated LDL is then digested with various non-specific proteases to remove the LDL while retaining the DNA. This DNA is  
20      then sequenced using standard sequencing techniques. A list of the DNA sequences along with the type of cancer it is associated with is made. This list is then used to synthesize probes that can differentiate among the various types of cancer. These probes are used in screening of a patient with an unknown cancer type, or in the early detection of metastatic cancer, or as a general early screening technique for the presence or absence of specific cancer types.

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**EXAMPLE 9****METHODS FOR THE DETERMINATION OF METASTATIC GENE TRANSFER VIA LIPOPROTEINS AS NATIVE VECTORS**

In order to determine the sequence of polynucleotides bound to endogenous LDL, plasma LDL and other apoB-containing lipoproteins are captured using a monoclonal antibody to a specific apoB epitope such as 2G8 which is immobilized on an inert, hydrophilic and highly porous polymer microbead. The LDL-DNA complex is then isolated by elution using affinity chromatography technology. DNA is further purified from the isolated LDL/DNA complex using standard DNA purification methodology such as phenol/chloroform extraction followed by ethanol precipitation. Alternatively, purified DNA is isolated from the affinity column using elution conditions that disrupt protein/DNA complexes but not protein/protein complexes (*i.e.*, antibody/LDL complex). The polynucleotide sequences are determined using the SRE, E/C, FAS, and ISRE-1A oligonucleotides (SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229, respectively) in a standard PCR<sup>TM</sup> methodology in order to amplify polynucleotides with unknown sequences. The amplified PCR<sup>TM</sup> products (*i.e.*, polynucleotides) are then isolated by agarose gel electrophoresis and subsequent DNA sequencing techniques well known to the art.

Alternatively, identification of polynucleotide sequences that are bound to endogenous human LDL is *via* the specific binding of LDL to a plastic matrix such as a 96 well ELISA (enzyme linked immunosorbant assay) plates coated with specific antibodies that bind to human LDL. In this embodiment, freshly isolated plasma containing endogenous lipoproteins is used to bind to the anti-human LDL antibodies using standard ELISA procedures lipoproteins to the art. The presence and specific sequence of polynucleotides prebound to the endogenous LDL in each is determined by PCR<sup>TM</sup> technology.

Because many varying and different embodiments may be made within the scope of the inventive concept herein taught, and because many modifications may be made in the embodiments herein detailed in accordance with the descriptive requirement of the law, it is to

be understood that the details herein are to be interpreted as illustrative and not in a limiting sense.

#### EXAMPLE 10

#### 5           LOW-DENSITY LIPOPROTEIN INTERACTS WITH           HUMAN CYTOMEGALOVIRUS GENOMIC DNA

DNA binding experiments with purified plasma lipoprotein fractions and human genomic DNA as well as several different plasmids indicate that purified LDL binds to human genomic DNA digested with different restriction enzymes (Alu I and Hind III).

10           Purified LDL also bound to several different plasmids but its binding affinity for plasmid DNA containing the HCMV IE promotor region was significantly higher. It was shown that the binding of both LDL and VLDL to the HCMV IE promotor region and SRE, MSRE, ISRE, MISRE, E/C, FAS, and MFAS oligonucleotides. The E/C oligonucleotide was used in these DNA binding studies because this oligonucleotide contains both a binding site for members of the C/EBP transcription factor family, which are involved in the regulation of differentiation-dependent adipocyte gene expression, as well as an overlapping E-box motif which is generally recognized by the eukaryotic basic helix-loop-helix (b-HLH) transcriptional regulators. LDL clearly have a greater affinity for all of the oligonucleotides tested than do VLDL. This is most likely due to interference with protein-DNA interaction caused by either the presence of other apolipoproteins on the surface of VLDL or an increased net charge as a result of the increased lipid content of VLDL.

25           The sequence specificity is illustrated by the fact that both LDL and VLDL show a decreased binding affinity for the mutated versions of the ISRE and FAS oligos (MISRE and MFAS respectively). In contrast, LDL showed an increased binding affinity for the mutated version of the SRE oligo (MSRE). It is possible that this mutated SRE sequence may be a better ligand for the putative DNA binding region of apo B present on LDL. The binding of both VLDL and LDL to the E/C oligonucleotide is not surprising since this oligo contains the

- 83 -

E-box motif which is a known binding site for b-HLH proteins and similar b-HLH regions have been identified in apoB present on VLDL and LDL.

The affinity for the HCMV IE promotor is not immediately obvious since careful analysis does not reveal an exact copy of either a SRE, ISRE, FAS, or E/C sequence. However, the HCMV IE promotor region contains regulatory elements that are generally recognized by a large number of eukaryotic DNA-binding proteins, including a variety of different families of transcription factors, and it may therefore be possible that the identified b-HLH regions of apoB possess similar DNA binding properties.

Another possibility is that other yet unidentified regions of apoB are involved in the binding to the HCMV IE promotor region. The fact that HDL in contrast to VLDL and LDL do not bind to any of the oligos tested suggests that the DNA binding results from the specific interaction with apo B. These data support the hypothesis that apo B contains DNA binding domains which show homology with the DNA binding domains of SREBP-1, SREBP-2, ADD-1, and ISGF3 $\gamma$  and that apo B containing lipoproteins therefore bind to specific nucleotide sequences similar to those bound by these known DNA binding proteins.

Recent reports suggest a possible causal relationship between human cytomegalovirus (HCMV) and the development of atherosclerosis in humans. These reports together with data presented herein, which show that human LDL binds strongly to HCMV IE promotor sequences, led the inventors to investigate whether plasma LDL may play a role in the pathogenesis of HCMV induced atherosclerosis.

To test this hypothesis, the inventors looked for HCMV DNA sequences in the purified plasma LDL fraction of human subjects who tested seropositive for HCMV by polymerase chain reaction (PCR). The results of these studies show that a PCR product of the expected size (170 bp) could be detected with both primer sets (MTR2 and IE) in the purified plasma LDL fraction of HCMV seropositive subjects. However, this 170 bp DNA fragment could not be detected in the plasma samples of these subjects (lanes 6-8). These data suggest that the use of purified plasma LDL fractions for detection of CMV nucleic acid sequences by PCR techniques

is more sensitive than when whole plasma samples are used. Furthermore, the increased yield of PCR products of the purified plasma LDL fractions strongly suggest that HCMV DNA is predominantly associated with LDL within the plasma pool of HCMV seropositive subjects.

5

## **EXAMPLE 11**

### **LOW-DENSITY LIPOPROTEIN AS A NATURAL GENE TRANSFER VECTOR**

The discovery of the nucleic acid-binding properties apo B-100 suggested that lipoproteins containing apoB100, as naturally occurring liposomes, may function as gene transfer agents. By using highly purified low-density lipoprotein as such an agent, the inventors were able to transfect cultured human skin fibroblasts *in vitro* and to express a green fluorescent protein reporter gene *in vivo*. The gene transfer mediated by low-density lipoprotein was more efficient than that mediated by LipoFectin. Low-density lipoprotein also did not exhibit any toxicity, immunogenicity, or serum inhibition.

15

#### **1. DNA-binding**

In the Examples above, it was shown that highly purified human LDL binds to nucleic acids in a specific fashion. In order to establish whether rat lipoproteins can bind nucleic acids in a similar fashion, DNA-binding experiments with different rat lipoprotein fractions were performed. A gel shift assay of linearized pBluescript KS and pBKCMV plasmid DNA and purified rat VLDL, LDL, and HDL fractions was performed. The data clearly demonstrate that the binding of nucleic acids is specific to the purified LDL fraction.

The binding of LDL to DNA is exhibited by the retarded electrophoretic migration of DNA in agarose gel that is caused by the formation of complexes of higher molecular weight. In contrast, purified fractions of VLDL and HDL did not bind any of the DNA samples tested. The fact that purified HDL did not bind DNA was expected, since endogenous HDL does not contain apo B-100. Surprisingly, there was no apparent binding of DNA to apo B-100-containing VLDL. It is possible that the DNA-binding assay, which employs ethidium bromide staining to detect DNA, lacks sensitivity or that VLDL does not bind to DNA under the conditions of the DNA-binding assay. Another explanation could be a difference in the

conformation of apo B-100 present on LDL as opposed to VLDL because of a difference in the lipid composition and protein content of the two lipoprotein fractions.

2. *In vitro* cell transfection studies.

5 Based on the findings of the DNA-binding assay, transfection studies were performed using a prebound complex of LDL and plasmid DNA that contained a reporter gene that encodes GFP.

10 The data generated illustrated the successful transfection of how human skin fibroblasts with LDL and pEGFP-N1 plasmid DNA. The transfection process was monitored by expression of the GFP encoding gene and is driven by the HCMV IE promoter. In addition to fluorescent microscopic analysis, expression of GFP was confirmed by a qualitative ELISA using a primary antibody against recombinant GFP and an HRP-conjugated secondary antibody with  $\sigma$ -phenylenediamine as a chromogenic substrate.

15 Human skin fibroblasts transfected with LDL exhibited a significantly lower intensity of green fluorescence than did cells transfected with LipoFectin, indicating that the level of GFP expression was lower in these LDL-transfected cells. When the percentage of positively transfected cells were compared, however, transfection with LDL yielded a higher percentage of transfected cells than did transfection with LipoFectin (20 to 30% and 60 to 70%, respectively).  
20 In addition, LipoFectin-mediated transfection resulted in green fluorescence in the cell cytoplasm and in the nuclei, whereas LDL-mediated transfection resulted in green fluorescence predominantly in the cytoplasm.

25 Transfection assays in which LDL concentrations were as high as 250 g/ml of LDL protein produced no detectable effects on the confluence and viability of the cell cultures, whereas LipoFectin concentrations of 20 g/ml resulted in significant loss of cell viability. Control cells that were transfected with linearized pEGFP-N1 plasmid DNA only exhibited no fluorescence.

3. *In vivo reporter gene expression.*

To evaluate whether LDL could be used as a vehicle for *in vivo* gene delivery, a prebound rat LDL-pEGFP-N1 complex was administered to 2-month-old female Sprague-Dawley rats. Cryosections of the liver and heart tissues of the treated animals that had been excised 2 days after the LDL-pEGFP-N1 complex showed significant levels of green fluorescence indicative of EGFP expression as determined by fluorescent microscopy.

The expression of GFP in the different tissues was confirmed by a qualitative ELISA using a primary antibody against recombinant GFP and an HRP-conjugated secondary antibody with  $\sigma$ -phenylenediamine as a chromogenic substrate. In contrast, only low levels of autofluorescence were observed in the cryosectioned tissues obtained from the control animals treated solely with linearized pEGFP-N1 DNA. These data demonstrate that purified LDL can be used in a prebound complex with DNA as an *in vivo* gene delivery system.

15

\* \* \*

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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- U.S. Patent No. 4,497,796
- U.S. Patent No. 4,663,292
- U.S. Patent No. 4,868,116
- 10     U.S. Patent No. 4,885,248
- U.S. Patent No. 4,904,582
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25

- 91 -

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(ii) TITLE OF INVENTION: LIPOPROTEINS AS NUCLEIC ACID VECTORS

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- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

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- 92 -

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(2) INFORMATION FOR SEQ ID NO: 1:

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(A) LENGTH: 4536 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Glu	Glu	Glu	Met	Leu	Glu	Asn	Val	Ser	Leu	Val	Cys	Pro	Lys	Asp	Ala
1					5				10				15		
Thr	Arg	Phe	Lys	His	Leu	Arg	Lys	Tyr	Thr	Tyr	Asn	Tyr	Glu	Ala	Glu
		20					25				30				
Ser	Ser	Ser	Gly	Val	Pro	Gly	Thr	Ala	Asp	Ser	Arg	Ser	Ala	Thr	Arg
		35				40				45					
Ile	Asn	Cys	Lys	Val	Glu	Leu	Glu	Val	Pro	Gln	Leu	Cys	Ser	Phe	Ile
		50			55			60							
Leu	Lys	Thr	Ser	Gln	Cys	Thr	Leu	Lys	Glu	Val	Tyr	Gly	Phe	Asn	Pro
	65				70			75			80				
Glu	Gly	Lys	Ala	Leu	Leu	Lys	Lys	Thr	Lys	Asn	Ser	Glu	Glu	Phe	Ala
		85				90			95						
Ala	Ala	Met	Ser	Arg	Tyr	Glu	Leu	Lys	Leu	Ala	Ile	Pro	Glu	Gly	Lys
		100				105			110						
Gln	Val	Phe	Leu	Tyr	Pro	Glu	Lys	Asp	Glu	Pro	Thr	Tyr	Ile	Leu	Asn
		115			120			125							
Ile	Lys	Arg	Gly	Ile	Ile	Ser	Ala	Leu	Leu	Val	Pro	Pro	Glu	Thr	Glu
	130				135			140							
Glu	Ala	Lys	Gln	Val	Leu	Phe	Leu	Asp	Thr	Val	Tyr	Gly	Asn	Cys	Ser
	145				150			155			160				
Thr	His	Phe	Thr	Val	Lys	Thr	Arg	Lys	Gly	Asn	Val	Ala	Thr	Glu	Ile
		165				170			175						
Ser	Thr	Glu	Arg	Asp	Leu	Gly	Gln	Cys	Asp	Arg	Phe	Lys	Pro	Ile	Arg
		180				185			190						
Thr	Gly	Ile	Ser	Pro	Leu	Ala	Leu	Ile	Lys	Gly	Met	Thr	Arg	Pro	Leu
		195				200			205						

- 93 -

Ser Thr Leu Ile Ser Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala  
210 215 220

Lys Arg Lys His Val Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe  
225 230 235 240

Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val Thr  
245 250 255

Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe  
260 265 270

Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser  
275 280 285

Thr Ser Pro Pro Lys Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu  
290 295 300

Leu Lys Lys Leu Thr Ile Ser Glu Gln Asn Ile Gin Arg Ala Asn Leu  
305 310 315 320

Phe Asn Lys Leu Val Thr Glu Leu Arg Gly Leu Ser Asp Glu Ala Val  
325 330 335

Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu  
340 345 350

Gln Ala Leu Val Gln Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu  
355 360 365

Gln Trp Leu Lys Arg Val His Ala Asn Pro Leu Leu Ile Asp Val Val  
370 375 380

Thr Tyr Leu Val Ala Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg  
385 390 395 400

Glu Ile Phe Asn Met Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr  
405 410 415

Ala Leu Ser His Ala Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly  
420 425 430

Thr Gln Glu Leu Leu Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln  
435 440 445

Asp Asp Cys Thr Gly Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val  
450 455 460

Ile Gly Asn Met Gly Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys  
465 470 475 480

Ser Ser Ile Leu Lys Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile  
485 490 495

- 94 -

Gln Lys Ala Ala Ile Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys  
500 505 510

Asp Gln Glu Val Leu Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly  
515 520 525

Asp Lys Arg Leu Ala Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln  
530 535 540

Ala Asp Ile Asn Lys Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu  
545 550 555 560

Gln Val Lys Asn Phe Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser  
565 570 575

Glu Glu Leu Asp Ile Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu  
580 585 590

Lys Glu Ser Gln Leu Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg  
595 600 605

Asn Tyr Gln Leu Tyr Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala  
610 615 620

Ser Ala Lys Ile Glu Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu  
625 630 635 640

Pro Lys Glu Ser Met Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala  
645 650 655

Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro  
660 665 670

Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val  
675 680 685

Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser  
690 695 700

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu  
705 710 715 720

Gln Asp Met Val Asn Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys  
725 730 735

Asp Leu Lys Ser Lys Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile  
740 745 750

Leu Gly Glu Glu Leu Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu  
755 760 765

Gly Lys Leu Leu Leu Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln  
770 775 780

- 95 -

Met Ile Gly Glu Val Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu  
785 790 795 800

His Tyr Ile Phe Met Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly  
805 810 815

Leu Gln Leu Gln Ile Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys  
820 825 830

Ala Gly Val Lys Leu Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala  
835 840 845

Lys Pro Ser Val Ser Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile  
850 855 860

Pro Asp Phe Ala Arg Ser Gly Val Gln Met Asn Thr Asn Phe Phe His  
865 870 875 880

Glu Ser Gly Leu Glu Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys  
885 890 895

Phe Ile Ile Pro Ser Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly  
900 905 910

Asn Thr Leu His Leu Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro  
915 920 925

Leu Ile Glu Asn Arg Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro  
930 935 940

Gly Leu Asn Tyr Cys Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr  
945 950 955 960

Asp Ser Ala Ser Tyr Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu  
965 970 975

Glu Leu Arg Pro Thr Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr  
980 985 990

Tyr Glu Leu Gln Arg Glu Asp Arg Ala Leu Val Asp Thr Leu Lys Phe  
995 1000 1005

Val Thr Gln Ala Glu Gly Ala Lys Gln Thr Glu Ala Thr Met Thr Phe  
1010 1015 1020

Lys Tyr Asn Arg Gln Ser Met Thr Leu Ser Ser Glu Val Gln Ile Pro  
1025 1030 1035 1040

Asp Phe Asp Val Asp Leu Gly Thr Ile Leu Arg Val Asn Asp Glu Ser  
1045 1050 1055

Thr Glu Gly Lys Thr Ser Tyr Arg Leu Thr Leu Asp Ile Gln Asn Lys  
1060 1065 1070

- 96 -

Lys Ile Thr Glu Val Ala Leu Met Gly His Leu Ser Cys Asp Thr Lys  
1075 1080 1085

Glu Glu Arg Lys Ile Lys Gly Val Ile Ser Ile Pro Arg Leu Gln Ala  
1090 1095 1100

Glu Ala Arg Ser Glu Ile Leu Ala His Trp Ser Pro Ala Lys Leu Leu  
1105 1110 1115 1120

Leu Gln Met Asp Ser Ser Ala Thr Ala Tyr Gly Ser Thr Val Ser Lys  
1125 1130 1135

Arg Val Ala Trp His Tyr Asp Glu Glu Lys Ile Glu Phe Glu Trp Asn  
1140 1145 1150

Thr Gly Thr Asn Val Asp Thr Lys Lys Met Thr Ser Asn Phe Pro Val  
1155 1160 1165

Asp Leu Ser Asp Tyr Pro Lys Ser Leu His Met Tyr Ala Asn Arg Leu  
1170 1175 1180

Leu Asp His Arg Val Pro Glu Thr Asp Met Thr Phe Arg His Val Gly  
1185 1190 1195 1200

Ser Lys Leu Ile Val Ala Met Ser Ser Trp Leu Gln Lys Ala Ser Gly  
1205 1210 1215

Ser Leu Pro Tyr Thr Gln Thr Leu Gln Asp His Leu Asn Ser Leu Lys  
1220 1225 1230

Glu Phe Asn Leu Gln Asn Met Gly Leu Pro Asp Phe His Ile Pro Glu  
1235 1240 1245

Asn Leu Phe Leu Lys Ser Asp Gly Arg Val Lys Tyr Thr Leu Asn Lys  
1250 1255 1260

Asn Ser Leu Lys Ile Glu Ile Pro Leu Pro Phe Gly Gly Lys Ser Ser  
1265 1270 1275 1280

Arg Asp Leu Lys Met Leu Glu Thr Val Arg Thr Pro Ala Leu His Phe  
1285 1290 1295

Lys Ser Val Gly Phe His Leu Pro Ser Arg Glu Phe Gln Val Pro Thr  
1300 1305 1310

Phe Thr Ile Pro Lys Leu Tyr Gln Leu Gln Val Pro Leu Leu Gly Val  
1315 1320 1325

Leu Asp Leu Ser Thr Asn Val Tyr Ser Asn Leu Tyr Asn Trp Ser Ala  
1330 1335 1340

Ser Tyr Ser Gly Gly Asn Thr Ser Thr Asp His Phe Ser Leu Arg Ala  
1345 1350 1355 1360

- 97 -

Arg Tyr His Met Lys Ala Asp Ser Val Val Asp Leu Leu Ser Tyr Asn  
 1365 1370 1375  
 Val Gln Gly Ser Gly Glu Thr Thr Tyr Asp His Lys Asn Thr Phe Thr  
 1380 1385 1390  
 Leu Ser Cys Asp Gly Ser Leu Arg His Lys Phe Leu Asp Ser Asn Ile  
 1395 1400 1405  
 Lys Phe Ser His Val Glu Lys Leu Gly Asn Asn Pro Val Ser Lys Gly  
 1410 1415 1420  
 Leu Leu Ile Phe Asp Ala Ser Ser Trp Gly Pro Gln Met Ser Ala  
 1425 1430 1435 1440  
 Ser Val His Leu Asp Ser Lys Lys Gln His Leu Phe Val Lys Glu  
 1445 1450 1455  
 Val Lys Ile Asp Gly Gln Phe Arg Val Ser Ser Phe Tyr Ala Lys Gly  
 1460 1465 1470  
 Thr Tyr Gly Leu Ser Cys Gln Arg Asp Pro Asn Thr Gly Arg Leu Asn  
 1475 1480 1485  
 Gly Glu Ser Asn Leu Arg Phe Asn Ser Ser Tyr Leu Gln Gly Thr Asn  
 1490 1495 1500  
 Gln Ile Thr Gly Arg Tyr Glu Asp Gly Thr Leu Ser Leu Thr Ser Thr  
 1505 1510 1515 1520  
 Ser Asp Leu Gln Ser Gly Ile Ile Lys Asn Thr Ala Ser Leu Lys Tyr  
 1525 1530 1535  
 Glu Asn Tyr Glu Leu Thr Leu Lys Ser Asp Thr Asn Gly Lys Tyr Lys  
 1540 1545 1550  
 Asn Phe Ala Thr Ser Asn Lys Met Asp Met Thr Phe Ser Lys Gln Asn  
 1555 1560 1565  
 Ala Leu Leu Arg Ser Glu Tyr Gln Ala Asp Tyr Glu Ser Leu Arg Phe  
 1570 1575 1580  
 Phe Ser Leu Leu Ser Gly Ser Leu Asn Ser His Gly Leu Glu Leu Asn  
 1585 1590 1595 1600  
 Ala Asp Ile Leu Gly Thr Asp Lys Ile Asn Ser Gly Ala His Lys Ala  
 1605 1610 1615  
 Thr Leu Arg Ile Gly Gln Asp Gly Ile Ser Thr Ser Ala Thr Thr Asn  
 1620 1625 1630  
 Leu Lys Cys Ser Leu Leu Val Leu Glu Asn Glu Leu Asn Ala Glu Leu  
 1635 1640 1645

- 98 -

Gly Leu Ser Gly Ala Ser Met Lys Leu Thr Thr Asn Gly Arg Phe Arg  
 1650 1655 1660  
 Glu His Asn Ala Lys Phe Ser Leu Asp Gly Lys Ala Ala Leu Thr Glu  
 1665 1670 1675 1680  
 Leu Ser Leu Gly Ser Ala Tyr Gln Ala Met Ile Leu Gly Val Asp Ser  
 1685 1690 1695  
 Lys Asn Ile Phe Asn Phe Lys Val Ser Gln Glu Gly Leu Lys Leu Ser  
 1700 1705 1710  
 Asn Asp Met Met Gly Ser Tyr Ala Glu Met Lys Phe Asp His Thr Asn  
 1715 1720 1725  
 Ser Leu Asn Ile Ala Gly Leu Ser Leu Asp Phe Ser Ser Lys Leu Asp  
 1730 1735 1740  
 Asn Ile Tyr Ser Ser Asp Lys Phe Tyr Lys Gln Thr Val Asn Leu Gln  
 1745 1750 1755 1760  
 Leu Gln Pro Tyr Ser Leu Val Thr Thr Leu Asn Ser Asp Leu Lys Tyr  
 1765 1770 1775  
 Asn Ala Leu Asp Leu Thr Asn Asn Gly Lys Leu Arg Leu Glu Pro Leu  
 1780 1785 1790  
 Lys Leu His Val Ala Gly Asn Leu Lys Gly Ala Tyr Gln Asn Asn Glu  
 1795 1800 1805  
 Ile Lys His Ile Tyr Ala Ile Ser Ser Ala Ala Leu Ser Ala Ser Tyr  
 1810 1815 1820  
 Lys Ala Asp Thr Val Ala Lys Val Gln Gly Val Glu Phe Ser His Arg  
 1825 1830 1835 1840  
 Leu Asn Thr Asp Ile Ala Gly Leu Ala Ser Ala Ile Asp Met Ser Thr  
 1845 1850 1855  
 Asn Tyr Asn Ser Asp Ser Leu His Phe Ser Asn Val Phe Arg Ser Val  
 1860 1865 1870  
 Met Ala Pro Phe Thr Met Thr Ile Asp Ala His Thr Asn Gly Asn Gly  
 1875 1880 1885  
 Lys Leu Ala Leu Trp Gly Glu His Thr Gly Gln Leu Tyr Ser Lys Phe  
 1890 1895 1900  
 Leu Leu Lys Ala Glu Pro Leu Ala Phe Thr Phe Ser His Asp Tyr Lys  
 1905 1910 1915 1920  
 Gly Ser Thr Ser His His Leu Val Ser Arg Lys Ser Ile Ser Ala Ala  
 1925 1930 1935

- 99 -

Leu Glu His Lys Val Ser Ala Leu Leu Thr Pro Ala Glu Gln Thr Gly  
 1940 1945 1950  
 Thr Trp Lys Leu Lys Thr Gln Phe Asn Asn Asn Glu Tyr Ser Gln Asp  
 1955 1960 1965  
 Leu Asp Ala Tyr Asn Thr Lys Asp Lys Ile Gly Val Glu Leu Thr Gly  
 1970 1975 1980  
 Arg Thr Leu Ala Asp Leu Thr Leu Leu Asp Ser Pro Ile Lys Val Pro  
 1985 1990 1995 2000  
 Leu Leu Leu Ser Glu Pro Ile Asn Ile Ile Asp Ala Leu Glu Met Arg  
 2005 2010 2015  
 Asp Ala Val Glu Lys Pro Gln Glu Phe Thr Ile Val Ala Phe Val Lys  
 2020 2025 2030  
 Tyr Asp Lys Asn Gln Asp Val His Ser Ile Asn Leu Pro Phe Phe Glu  
 2035 2040 2045  
 Thr Leu Gln Glu Tyr Phe Glu Arg Asn Arg Gln Thr Ile Ile Val Val  
 2050 2055 2060  
 Val Glu Asn Val Gln Arg Asn Leu Lys His Ile Asn Ile Asp Gln Phe  
 2065 2070 2075 2080  
 Val Arg Lys Tyr Arg Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn  
 2085 2090 2095  
 Asp Tyr Leu Asn Ser Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys  
 2100 2105 2110  
 Glu Lys Leu Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp  
 2115 2120 2125  
 Ile Gln Ile Ala Leu Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu  
 2130 2135 2140  
 Ser Gln Leu Gln Thr Tyr Met Ile Gln Phe Asp Gln Tyr Ile Lys Asp  
 2145 2150 2155 2160  
 Ser Tyr Asp Leu His Asp Leu Lys Ile Ala Ile Ala Asn Ile Ile Asp  
 2165 2170 2175  
 Glu Ile Ile Glu Lys Leu Lys Ser Leu Asp Glu His Tyr His Ile Arg  
 2180 2185 2190  
 Val Asn Leu Val Lys Thr Ile His Asp Leu His Leu Phe Ile Glu Asn  
 2195 2200 2205  
 Ile Asp Phe Asn Lys Ser Gly Ser Ser Thr Ala Ser Trp Ile Gln Asn  
 2210 2215 2220

- 100 -

Val Asp Thr Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln  
2225                    2230                    2235                    2240

Gln Leu Lys Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly  
2245                    2250                    2255

Lys Leu Lys Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp  
2260                    2265                    2270

Gln Leu Gly Thr Thr Ile Ser Phe Glu Arg Ile Asn Asp Val Leu Glu  
2275                    2280                    2285

His Val Lys His Phe Val Ile Asn Leu Ile Gly Asp Phe Glu Val Ala  
2290                    2295                    2300

Glu Lys Ile Asn Ala Phe Arg Ala Lys Val His Glu Leu Ile Glu Arg  
2305                    2310                    2315                    2320

Tyr Glu Val Asp Gln Gln Ile Gln Val Leu Met Asp Lys Leu Val Glu  
2325                    2330                    2335

Leu Thr His Gln Tyr Lys Leu Lys Glu Thr Ile Gln Lys Leu Ser Asn  
2340                    2345                    2350

Val Leu Gln Gln Val Lys Ile Lys Asp Tyr Phe Glu Lys Leu Val Gly  
2355                    2360                    2365

Phe Ile Asp Asp Ala Val Lys Lys Leu Asn Glu Leu Ser Phe Lys Thr  
2370                    2375                    2380

Phe Ile Glu Asp Val Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu  
2385                    2390                    2395                    2400

Lys Ser Phe Asp Tyr His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile  
2405                    2410                    2415

Arg Glu Val Thr Gln Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu  
2420                    2425                    2430

Pro Gln Lys Ala Glu Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala  
2435                    2440                    2445

Thr Val Ala Val Tyr Leu Glu Ser Leu Gln Asp Thr Lys Ile Thr Leu  
2450                    2455                    2460

Ile Ile Asn Trp Leu Gln Glu Ala Leu Ser Ser Ala Ser Leu Ala His  
2465                    2470                    2475                    2480

Met Lys Ala Lys Phe Arg Glu Thr Leu Glu Asp Thr Arg Asp Arg Met  
2485                    2490                    2495

Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val  
2500                    2505                    2510

- 101 -

Gly Gln Val Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr  
2515 2520 2525

Leu Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln  
2530 2535 2540

Asp Trp Ala Lys Arg Met Lys Ala Leu Val Glu Gln Gly Phe Thr Val  
2545 2550 2555 2560

Pro Glu Ile Lys Thr Ile Leu Gly Thr Met Pro Ala Phe Glu Val Ser  
2565 2570 2575

Leu Gln Ala Leu Gln Lys Ala Thr Phe Gln Thr Pro Asp Phe Ile Val  
2580 2585 2590

Pro Leu Thr Asp Leu Arg Ile Pro Ser Val Gln Ile Asn Phe Lys Asp  
2595 2600 2605

Leu Lys Asn Ile Lys Ile Pro Ser Arg Phe Ser Thr Pro Glu Phe Thr  
2610 2615 2620

Ile Leu Asn Thr Phe His Ile Pro Ser Phe Thr Ile Asp Phe Val Glu  
2625 2630 2635 2640

Met Lys Val Lys Ile Ile Arg Thr Ile Asp Gln Met Gln Asn Ser Glu  
2645 2650 2655

Leu Gln Trp Pro Val Pro Asp Ile Tyr Leu Arg Asp Leu Lys Val Glu  
2660 2665 2670

Asp Ile Pro Leu Ala Arg Ile Thr Leu Pro Asp Phe Arg Leu Pro Glu  
2675 2680 2685

Ile Ala Ile Pro Glu Phe Ile Ile Pro Thr Leu Asn Leu Asn Asp Phe  
2690 2695 2700

Gln Val Pro Asp Leu His Ile Pro Glu Phe Gln Leu Pro His Ile Ser  
2705 2710 2715 2720

His Thr Ile Glu Val Pro Thr Phe Gly Lys Leu Tyr Ser Ile Leu Lys  
2725 2730 2735

Ile Gln Ser Pro Leu Phe Thr Leu Asp Ala Asn Ala Asp Ile Gly Asn  
2740 2745 2750

Gly Thr Thr Ser Ala Asn Glu Ala Gly Ile Ala Ala Ser Ile Thr Ala  
2755 2760 2765

Lys Gly Glu Ser Lys Leu Glu Val Leu Asn Phe Asp Phe Gln Ala Asn  
2770 2775 2780

Ala Gln Leu Ser Asn Pro Lys Ile Asn Pro Leu Ala Leu Lys Glu Ser  
2785 2790 2795 2800

- 102 -

Val Lys Phe Ser Ser Lys Tyr Leu Arg Thr Glu His Gly Ser Glu Met  
2805 2810 2815

Leu Phe Phe Gly Asn Ala Ile Glu Gly Lys Ser Asn Thr Val Ala Ser  
2820 2825 2830

Leu His Thr Glu Lys Asn Thr Leu Glu Leu Ser Asn Gly Val Ile Val  
2835 2840 2845

Lys Ile Asn Asn Gln Leu Thr Leu Asp Ser Asn Thr Lys Tyr Phe His  
2850 2855 2860

Lys Leu Asn Ile Pro Lys Leu Asp Phe Ser Ser Gln Ala Asp Leu Arg  
2865 2870 2875 2880

Asn Glu Ile Lys Thr Leu Leu Lys Ala Gly His Ile Ala Trp Thr Ser  
2885 2890 2895

Ser Gly Lys Gly Ser Trp Lys Trp Ala Cys Pro Arg Phe Ser Asp Glu  
2900 2905 2910

Gly Thr His Glu Ser Gln Ile Ser Phe Thr Ile Glu Gly Pro Leu Thr  
2915 2920 2925

Ser Phe Gly Leu Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn  
2930 2935 2940

Gln Asn Leu Val Tyr Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu  
2945 2950 2955 2960

Ile Gln Ser Gln Val Asp Ser Gln His Val Gly His Ser Val Leu Thr  
2965 2970 2975

Ala Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly  
2980 2985 2990

Arg His Asp Ala His Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn  
2995 3000 3005

Ser Leu Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn  
3010 3015 3020

Asn Glu Gly Asn Leu Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys  
3025 3030 3035 3040

Ile Asp Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln  
3045 3050 3055

Gln Ala Ser Trp Gln Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn  
3060 3065 3070

Gln Asn Phe Ser Ala Gly Asn Asn Glu Asn Ile Met Glu Ala His Val  
3075 3080 3085

- 103 -

Gly Ile Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr  
3090 3095 3100

Ile Pro Glu Met Arg Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu  
3105 3110 3115 3120

Lys Asp Phe Ser Leu Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys  
3125 3130 3135

Thr Thr Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys  
3140 3145 3150

Asn Lys His Arg His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu  
3155 3160 3165

Phe Ile Ser Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn  
3170 3175 3180

Arg Asn Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys  
3185 3190 3195 3200

Ile Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro  
3205 3210 3215

Arg Thr Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu  
3220 3225 3230

Val Ser Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro  
3235 3240 3245

Lys Ala Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg  
3250 3255 3260

Val Pro Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu  
3265 3270 3275 3280

His Val Pro Arg Asn Leu Lys Leu Ser Leu Pro His Phe Lys Glu Leu  
3285 3290 3295

Cys Thr Ile Ser His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr  
3300 3305 3310

Asp Phe Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu  
3315 3320 3325

Leu Phe Asn Gln Ser Asp Ile Val Ala His Leu Leu Ser Ser Ser  
3330 3335 3340

Ser Val Ile Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu  
3345 3350 3355 3360

Thr Arg Lys Arg Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn  
3365 3370 3375

- 104 -

Lys	Phe	Val	Glu	Gly	Ser	His	Asn	Ser	Thr	Val	Ser	Leu	Thr	Thr	Lys
3380															3390
Asn	Met	Glu	Val	Ser	Val	Ala	Lys	Thr	Thr	Lys	Ala	Glu	Ile	Pro	Ile
3395															3405
Leu	Arg	Met	Asn	Phe	Lys	Gln	Glu	Leu	Asn	Gly	Asn	Thr	Lys	Ser	Lys
3410															3420
Pro	Thr	Val	Ser	Ser	Ser	Met	Glu	Phe	Lys	Tyr	Asp	Phe	Asn	Ser	Ser
3425															3440
Met	Leu	Tyr	Ser	Thr	Ala	Lys	Gly	Ala	Val	Asp	His	Lys	Leu	Ser	Leu
3445															3455
Glu	Ser	Leu	Thr	Ser	Tyr	Phe	Ser	Ile	Glu	Ser	Ser	Thr	Lys	Gly	Asp
3460															3470
Val	Lys	Gly	Ser	Val	Leu	Ser	Arg	Glu	Tyr	Ser	Gly	Thr	Ile	Ala	Ser
3475															3485
Glu	Ala	Asn	Thr	Tyr	Leu	Asn	Ser	Lys	Ser	Thr	Arg	Ser	Ser	Val	Lys
3490															3500
Leu	Gln	Gly	Thr	Ser	Lys	Ile	Asp	Asp	Ile	Trp	Asn	Leu	Glu	Val	Lys
3505															3520
Glu	Asn	Phe	Ala	Gly	Glu	Ala	Thr	Leu	Gln	Arg	Ile	Tyr	Ser	Leu	Trp
3525															3535
Glu	His	Ser	Thr	Lys	Asn	His	Leu	Gln	Leu	Glu	Gly	Leu	Phe	Phe	Thr
3540															3550
Asn	Gly	Glu	His	Thr	Ser	Lys	Ala	Thr	Leu	Glu	Leu	Ser	Pro	Trp	Gln
3555															3565
Met	Ser	Ala	Leu	Val	Gln	Val	His	Ala	Ser	Gln	Pro	Ser	Ser	Phe	His
3570															3580
Asp	Phe	Pro	Asp	Leu	Gly	Gln	Glu	Val	Ala	Leu	Asn	Ala	Asn	Thr	Lys
3585															3600
Asn	Gln	Lys	Ile	Arg	Trp	Lys	Asn	Glu	Val	Arg	Ile	His	Ser	Gly	Ser
3605															3615
Phe	Gln	Ser	Gln	Val	Glu	Leu	Ser	Asn	Asp	Gln	Glu	Lys	Ala	His	Leu
3620															3630
Asp	Ile	Ala	Gly	Ser	Leu	Glu	Gly	His	Leu	Arg	Phe	Leu	Lys	Asn	Ile
3635															3645
Ile	Leu	Pro	Val	Tyr	Asp	Lys	Ser	Leu	Trp	Asp	Phe	Leu	Lys	Leu	Asp
3650															3660

- 105 -

Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala			
3665	3670	3675	3680
Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val			
3685	3690	3695	
Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn Asp			
3700	3705	3710	
Leu Asn Ser Val Leu Val Met Pro Thr Phe His Val Pro Phe Thr Asp			
3715	3720	3725	
Leu Gln Val Pro Ser Cys Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr			
3730	3735	3740	
Lys Lys Leu Arg Thr Ser Ser Phe Ala Leu Asn Leu Pro Thr Leu Pro			
3745	3750	3755	3760
Glu Val Lys Phe Pro Glu Val Asp Val Leu Thr Lys Tyr Ser Gln Pro			
3765	3770	3775	
Glu Asp Ser Leu Ile Pro Phe Phe Glu Ile Thr Val Pro Glu Ser Gln			
3780	3785	3790	
Leu Thr Val Ser Gln Phe Thr Leu Pro Lys Ser Val Ser Asp Gly Ile			
3795	3800	3805	
Ala Ala Leu Asp Leu Asn Ala Val Ala Asn Lys Ile Ala Asp Phe Glu			
3810	3815	3820	
Leu Pro Thr Ile Ile Val Pro Glu Gln Thr Ile Glu Ile Pro Ser Ile			
3825	3830	3835	3840
Lys Phe Ser Val Pro Ala Gly Ile Val Ile Pro Ser Phe Gln Ala Leu			
3845	3850	3855	
Thr Ala Arg Phe Glu Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser			
3860	3865	3870	
Ala Ser Leu Lys Asn Lys Ala Asp Tyr Val Glu Thr Val Leu Asp Ser			
3875	3880	3885	
Thr Cys Ser Ser Thr Val Gln Phe Leu Glu Tyr Glu Leu Asn Val Leu			
3890	3895	3900	
Gly Thr His Lys Ile Glu Asp Gly Thr Leu Ala Ser Lys Thr Lys Gly			
3905	3910	3915	3920
Thr Leu Ala His Arg Asp Phe Ser Ala Glu Tyr Glu Glu Asp Gly Lys			
3925	3930	3935	
Phe Glu Gly Leu Gln Glu Trp Glu Gly Lys Ala His Leu Asn Ile Lys			
3940	3945	3950	

- 106 -

Ser Pro Ala Phe Thr Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys			
3955	3960	3965	
Gly Ile Ser Thr Ser Ala Ala Ser Pro Ala Val Gly Thr Val Gly Met			
3970	3975	3980	
Asp Met Asp Glu Asp Asp Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser			
3985	3990	3995	4000
Pro Gln Ser Ser Pro Asp Lys Lys Leu Thr Ile Phe Lys Thr Glu Leu			
4005	4010	4015	
Arg Val Arg Glu Ser Asp Glu Glu Thr Gln Ile Lys Val Asn Trp Glu			
4020	4025	4030	
Glu Glu Ala Ala Ser Gly Leu Leu Thr Ser Leu Lys Asp Asn Val Pro			
4035	4040	4045	
Lys Ala Thr Gly Val Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu			
4050	4055	4060	
His Thr Gly Leu Thr Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn			
4065	4070	4075	4080
Leu Gln Asn Asn Ala Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile			
4085	4090	4095	
Asp Asp Ile Asp Val Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly			
4100	4105	4110	
Thr Tyr Gln Glu Trp Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu			
4115	4120	4125	
Leu Thr Gln Glu Gly Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val			
4130	4135	4140	
Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His Met Lys Val Lys			
4145	4150	4155	4160
His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln			
4165	4170	4175	
Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met			
4180	4185	4190	
Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val			
4195	4200	4205	
His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile			
4210	4215	4220	
Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser			
4225	4230	4235	4240

- 107 -

Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val  
4245 4250 4255

Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu Val Leu Arg Asn Leu  
4260 4265 4270

Gln Asp Leu Leu Gln Phe Ile Phe Gln Leu Ile Glu Asp Asn Ile Lys  
4275 4280 4285

Gln Leu Lys Glu Met Lys Phe Thr Tyr Leu Ile Asn Tyr Ile Gln Asp  
4290 4295 4300

Glu Ile Asn Thr Ile Phe Asn Asp Tyr Ile Pro Tyr Val Phe Lys Leu  
4305 4310 4315 4320

Leu Lys Glu Asn Leu Cys Leu Asn Leu His Lys Phe Asn Glu Phe Ile  
4325 4330 4335

Gln Asn Glu Leu Gln Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln  
4340 4345 4350

Tyr Ile Met Ala Leu Arg Glu Glu Tyr Phe Asp Pro Ser Ile Val Gly  
4355 4360 4365

Trp Thr Val Lys Tyr Tyr Glu Leu Glu Glu Lys Ile Val Ser Leu Ile  
4370 4375 4380

Lys Asn Leu Leu Val Ala Leu Lys Asp Phe His Ser Glu Tyr Ile Val  
4385 4390 4395 4400

Ser Ala Ser Asn Phe Thr Ser Gln Leu Ser Ser Gln Val Glu Gln Phe  
4405 4410 4415

Leu His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp  
4420 4425 4430

Gly Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu  
4435 4440 4445

Ile Ile Lys Ser Gln Ala Ile Ala Thr Lys Lys Ile Ile Ser Asp Tyr  
4450 4455 4460

His Gln Gln Phe Arg Tyr Lys Leu Gln Asp Phe Ser Asp Gln Leu Ser  
4465 4470 4475 4480

Asp Tyr Tyr Glu Lys Phe Ile Ala Glu Ser Lys Arg Leu Ile Asp Leu  
4485 4490 4495

Ser Ile Gln Asn Tyr His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu  
4500 4505 4510

Lys Lys Leu Gln Ser Thr Thr Val Met Asn Pro Tyr Met Lys Leu Ala  
4515 4520 4525

- 108 -

Pro Gly Glu Leu Thr Ile Ile Leu  
4530                           4535

(2) INFORMATION FOR SEQ ID NO: 2:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 3 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Pro Xaa Pro  
1

(2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 46 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly  
1                         5   10   15  
Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val Glu Leu  
20                         25   30  
Glu Val Pro Gln Leu Cys Ser Phe Ile Leu Lys Thr Ser Gln  
35                         40   45

(2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 45 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ala Tyr Asp Phe Asn Tyr Pro Ile Lys Lys Asp Ser Ser Ser Gln Leu  
1                         5   10   15  
Leu Ser Val Gln Gln Gly Glu Thr Ile Tyr Ile Leu Asn Lys Asn Ser  
20                         25   30

- 109 -

Ser Gly Trp Trp Asp Gly Leu Val Ile Asp Asp Ser Asn  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 45 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys  
1 5 10 15

Asn Ser Glu Glu Phe Ala Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu  
20 25 30

Ala Ile Pro Glu Gly Lys Gln Val Phe Leu Tyr Pro Glu  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 6:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 47 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys  
1 5 10 15

Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Tyr Asn Gly Glu Trp  
20 25 30

Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 44 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

- 110 -

Phe Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val  
1 5 10 15

Thr Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe  
20 25 30

Phe Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe  
35 40

(2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 43 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Leu Phe Asp Tyr Lys Ala Gln Arg Glu Asp Glu Leu Thr Phe Thr Lys  
1 5 10 15

Ser Ala Ile Ile Gln Asn Val Glu Lys Gln Glu Gly Gly Trp Trp Arg  
20 25 30

Gly Asp Tyr Gly Gly Lys Lys Gln Leu Trp Phe  
35 40

(2) INFORMATION FOR SEQ ID NO: 9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 45 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Phe Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val  
1 5 10 15

Thr Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe  
20 25 30

Phe Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 46 amino acids
  - (B) TYPE: amino acid

- 111 -

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Leu His Ser Tyr Glu Pro Ser His Asp Gly Asp Leu Gly Phe Glu Lys  
1                   5   15  
  
Gly Glu Gln Leu Arg Ile Leu Glu Gln Ser Gly Glu Trp Trp Lys Ala  
20                   25   30  
  
Gln Ser Leu Thr Thr Gly Gln Glu Gly Phe Ile Pro Phe Asn  
35                   40    45

(2) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 62 amino acids
  - (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Tyr Thr Tyr Leu Ile Leu Arg Val Ile Gly Asn Met Gly Gln Thr Met  
1                   5   15  
  
Glu Gln Leu Thr Pro Glu Leu Lys Ser Ser Ile Leu Lys Cys Val Gln  
20                   25   30  
  
Ser Thr Lys Pro Ser Leu Met Ile Gln Lys Ala Ala Ile Gln Ala Leu  
35                   40    45  
  
Arg Lys Met Glu Pro Lys Asp Lys Asp Gln Glu Val Leu Leu  
50                   55    60

(2) INFORMATION FOR SEQ ID NO: 12:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 53 amino acids
  - (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Val Val Ala Leu Phe Asp Tyr Ala Ala Val Asn Asp Arg Asp Leu Gln  
1                   5   15  
  
Val Leu Lys Gly Glu Lys Leu Gln Val Leu Arg Ser Thr Gly Asp Trp  
20                   25   30

- 112 -

Trp Leu Ala Arg Ser Leu Val Thr Gly Arg Glu Gly Tyr Val Pro Ser  
35 40 45

Asn Phe Val Ala Pro  
50

(2) INFORMATION FOR SEQ ID NO: 13:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 50 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Ala Phe Gly Phe Ala Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly  
1 5 10 15

Lys Gly Phe Glu Pro Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe  
20 25 30

Phe Pro Asp Ser Val Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val  
35 40 45

Pro Asp  
50

(2) INFORMATION FOR SEQ ID NO: 14:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 48 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Leu Tyr Asp Phe Ala Ala Glu Asn Pro Asp Glu Leu Thr Phe Asn Glu  
1 5 10 15

Gly Ala Val Val Thr Val Ile Asn Lys Ser Asn Pro Asp Trp Trp Glu  
20 25 30

Gly Glu Leu Asn Gly Gln Arg Gly Val Phe Pro Ala Ser Tyr Val Glu  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 15:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 46 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:

- 113 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Phe Gly Tyr Thr Lys Asp Asp Lys His Glu Gln Asp Met Val Asn Gly  
1               5                           10                           15  
  
Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys Ser Lys Glu  
20   25                           30  
  
Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu Glu  
35   40                           45

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Tyr Asp Tyr Lys Lys Glu Glu Asp Ile Asp Leu His Leu Gly Asp  
1               5                           10                           15  
  
Ile Leu Thr Val Asn Lys Gly Ser Leu Val Ala Leu Gly Phe Ser Asp  
20   25                           30  
  
Gly Gln Glu Ala Lys Pro Glu Glu Ile Gly Trp Leu Asn Gly Tyr Asn  
35   40                           45

Glu

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Phe Asp Tyr His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu  
1               5                           10                           15  
  
Val Thr Gln Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro Gln  
20   25                           30  
  
Lys Ala Glu Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala Thr Val  
35   40                           45

- 114 -

Ala Val Tyr Leu  
50

(2) INFORMATION FOR SEQ ID NO: 18:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 46 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Tyr Asp Tyr Gln Glu Lys Ser Pro Arg Glu Val Thr Met Lys Lys Gly  
1                   5                   10                   15

Asp Ile Leu Thr Leu Leu Asn Ser Thr Asn Lys Asp Trp Trp Lys Val  
20                   25                   30

Glu Val Asn Asp Arg Gln Gly Phe Val Pro Ala Ala Tyr Val  
35                   40                   45

(2) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 51 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val  
1                   5                   10                   15

Gly Gln Val Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr  
20                   25                   30

Leu Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln  
35                   40                   45

Asp Trp Ala  
50

(2) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 51 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

**SUBSTITUTE SHEET (RULE 26)**

- 115 -

Phe Asp Tyr Lys Ala Gln Arg Glu Asp Glu Leu Thr Phe Thr Lys Ser  
1 5 10 15

Ala Ile Ile Gln Asn Val Glu Lys Gln Asp Gly Gly Trp Trp Arg Gly  
20 25 30

Asp Tyr Gly Gly Lys Lys Gln Leu Trp Phe Pro Ser Asn Tyr Val Glu  
35 40 45

Glu Met Ile  
50

(2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 55 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val  
1 5 10 15

Gly Gln Val Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr  
20 25 30

Leu Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln  
35 40 45

Asp Trp Ala Lys Arg Met Lys  
50 55

(2) INFORMATION FOR SEQ ID NO: 22:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 53 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Ile Gln Asp Tyr Glu Pro Arg Leu Thr Asp Glu Ile Arg Ile Ser Leu  
1 5 10 15

Gly Glu Lys Val Lys Ile Leu Ala Thr His Thr Asp Gly Trp Cys Leu  
20 25 30

Val Glu Lys Cys Asn Thr Arg Lys Gly Thr Ile His Val Ser Val Asp  
35 40 45

- 116 -

Asp Lys Arg Tyr Leu  
50

(2) INFORMATION FOR SEQ ID NO: 23:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 49 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Tyr Asp Tyr Glu Ala Arg Thr Glu Asp Asp Leu Thr Phe Thr Lys Gly  
1 5 10 15

Glu Lys Phe His Ile Leu Asn Asn Thr Glu Gly Asp Trp Trp Glu Ala  
20 25 30

Arg Ser Leu Ser Ser Gly Lys Thr Gly Cys Ile Pro Ser Asn Tyr Val  
35 40 45

Ala

(2) INFORMATION FOR SEQ ID NO: 24:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 45 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Thr Tyr Asp Phe Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn  
1 5 10 15

Ala Glu Leu Phe Asn Gln Ser Asp Ile Val Ala His Leu Leu Ser Ser  
20 25 30

Ser Ser Ser Val Ile Asp Ala Leu Gln Tyr Lys Leu Glu  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 25:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 47 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

**SUBSTITUTE SHEET (RULE 26)**

- 117 -

Asp Phe Asn Tyr Pro Ile Lys Lys Asp Ser Ser Ser Gln Leu Leu Ser  
1 5 10 15  
Val Gln Gln Gly Glu Thr Ile Tyr Ile Leu Asn Lys Asn Ser Ser Gly  
20 25 30  
Trp Trp Asp Gly Leu Val Ile Asp Asp Ser Asn Gly Lys Val Asn  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 26:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 49 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr Ser Thr Ala Lys Gly Ala  
1 5 10 15  
Val Asp His Lys Leu Ser Leu Glu Ser Leu Thr Ser Tyr Phe Ser Ile  
20 25 30  
Glu Ser Ser Thr Lys Gly Asp Val Lys Gly Ser Val Leu Ser Arg Glu  
35 40 45

Tyr

(2) INFORMATION FOR SEQ ID NO: 27:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 52 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Glu Pro Tyr Val Ala Ile Lys Ala Tyr Thr Ala Val Glu Gly Asp Glu  
1 5 10 15  
Val Ser Leu Leu Glu Gly Glu Ala Val Glu Val Ile His Lys Leu Leu  
20 25 30  
Asp Gly Trp Trp Val Ile Arg Lys Asp Asp Val Thr Gly Tyr Phe Pro  
35 40 45  
Ser Met Tyr Leu  
50

- 118 -

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 54 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg  
1 5 10 15

Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn  
20 25 30

Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile  
35 40 45

Thr Pro Gly Leu Lys Leu  
50

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 55 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Leu Tyr Asp Phe Lys Ala Glu Lys Ala Asp Glu Leu Thr Thr Tyr Val  
1 5 10 15

Gly Glu Asn Leu Phe Ile Cys Ala His His Asn Cys Glu Trp Phe Ile  
20 25 30

Ala Lys Pro Ile Gly Arg Leu Gly Gly Pro Gly Leu Val Pro Val Gly  
35 40 45

Phe Val Ser Ile Ile Asp Ile  
50 55

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

- 119 -

Val Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu  
1 5 10 15

Thr Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn  
20 25 30

Ala Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 31:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 40 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Val Leu Tyr Asp Phe Lys Ala Glu Lys Ala Asp Glu Leu Thr Thr Tyr  
1 5 10 15

Val Gly Glu Asn Leu Phe Ile Cys Ala His His Asn Cys Glu Trp Phe  
20 25 30

Ile Ala Lys Pro Ile Gly Arg Leu  
35 40

(2) INFORMATION FOR SEQ ID NO: 32:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 43 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met Phe Ile Arg  
1 5 10 15

Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val His Asn Gly  
20 25 30

Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu  
35 40

(2) INFORMATION FOR SEQ ID NO: 33:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 52 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:

- 120 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Gly Asn Ile Val Phe Val Leu Lys Lys Gly Asn Asp Asn Trp Ala Thr  
 20 25 30

Val Met Phe Asn Gly Gln Lys Gly Leu Val Pro Cys Asn Tyr Leu Glu  
35 40 45

Pro Val Glu Leu  
50

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val His Asn  
20 25 30

Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp  
35 40

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Ala Lys Phe Asp Tyr Val Ala Gln Gln Glu Gln Glu Leu Asp Ile Lys  
1 5 10 15

Lys Asn Glu Arg Leu Trp Leu Leu Asp Asp Ser Lys Ser Trp Trp Arg  
20 25 30

Val Arg Asn Ser Met Asn Lys Thr Gly Phe Val Pro Ser Asn Tyr Val  
35 40 45

- 121 -

Glu Arg Lys Asn  
50

(2) INFORMATION FOR SEQ ID NO: 36:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 85 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Trp Tyr His Ala Ser Leu Thr Arg Ala Gln Ala Glu His Met Leu Met  
1 5 10 15

Arg Val Pro Arg Asp Gly Ala Phe Leu Val Arg Lys Arg Asn Glu Pro  
20 25 30

Asn Ser Tyr Ala Ile Ser Phe Arg Ala Glu Gly Lys Ile Lys His Cys  
35 40 45

Arg Val Gln Gln Glu Gly Thr Val Met Leu Gly Asn Ser Glu Phe Asp  
50 55 60

Ser Leu Val Asp Leu Ile Ser Tyr Tyr Glu Lys His Pro Leu Tyr Arg  
65 70 75 80

Lys Met Lys Leu Lys  
85

(2) INFORMATION FOR SEQ ID NO: 37:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 106 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Phe Phe Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu Ser Thr  
1 5 10 15

Lys Ser Thr Ser Pro Pro Lys Gln Ala Glu Ala Val Leu Lys Thr Leu  
20 25 30

Gln Glu Leu Lys Lys Leu Thr Ile Ser Glu Gln Asn Ile Gln Arg Ala  
35 40 45

Asn Leu Phe Asn Lys Leu Val Thr Glu Leu Arg Gly Leu Ser Asp Glu  
50 55 60

- 122 -

Ala Val Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile			
65	70	75	80
Thr Leu Gln Ala Leu Val Gln Cys Gly Gln Pro Cys Ser Thr His Ile			
85	90	95	
Leu Gln Trp Leu Lys Arg Val His Ala Asn			
100	105		

(2) INFORMATION FOR SEQ ID NO: 38:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 91 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Trp Phe His Gly Lys Ile Ser Lys Gln Glu Ala Tyr Asn Leu Leu Met			
1	5	10	15
Thr Val Gly Gln Ala Cys Ser Phe Leu Val Arg Pro Ser Asp Asn Thr			
20	25	30	
Pro Gly Asp Tyr Ser Leu Tyr Phe Arg Thr Ser Glu Asn Ile Gln Arg			
35	40	45	
Phe Lys Ile Cys Pro Thr Pro Asn Asn Gln Phe Met Met Gly Gly Arg			
50	55	60	
Tyr Tyr Asn Ser Ser Ile Gly Asp Ile Ile Asp His Tyr Arg Lys Glu			
65	70	75	80
Gln Ile Val Glu Gly Tyr Tyr Leu Lys Glu Pro			
85	90		

(2) INFORMATION FOR SEQ ID NO: 39:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 93 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys Ser Lys Glu			
1	5	10	15
Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu Glu Leu Gly			
20	25	30	

- 123 -

Phe	Ala	Ser	Leu	His	Asp	Leu	Gln	Leu	Leu	Gly	Lys	Leu	Leu	Leu	Met
35						40					45				
Gly	Ala	Arg	Thr	Leu	Gln	Gly	Ile	Pro	Gln	Met	Ile	Gly	Glu	Val	Ile
50						55				60					
Arg	Lys	Gly	Ser	Lys	Asn	Asp	Phe	Phe	Leu	His	Tyr	Ile	Phe	Met	Glu
65						70				75				80	
Asn	Ala	Phe	Glu	Leu	Pro	Thr	Gly	Ala	Gly	Leu	Gln	Leu			
						85				90					

(2) INFORMATION FOR SEQ ID NO: 40:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 89 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Trp	Phe	His	Gly	Lys	Ile	Ser	Lys	Gln	Glu	Ala	Tyr	Asn	Leu	Leu	Met
1					5				10				15		
Thr	Val	Gly	Gln	Ala	Cys	Ser	Phe	Leu	Val	Arg	Pro	Ser	Asp	Asn	Thr
							20		25			30			
Pro	Gly	Asp	Tyr	Ser	Leu	Tyr	Phe	Arg	Thr	Ser	Glu	Asn	Ile	Gln	Arg
							35		40			45			
Phe	Lys	Ile	Cys	Pro	Thr	Pro	Asn	Asn	Gln	Phe	Met	Met	Gly	Gly	Arg
							50		55			60			
Tyr	Tyr	Asn	Ser	Ser	Ile	Gly	Asp	Ile	Ile	Asp	His	Tyr	Arg	Lys	Glu
							65		70			75		80	
Gln	Ile	Val	Glu	Gly	Tyr	Tyr	Leu	Lys							
							85								

(2) INFORMATION FOR SEQ ID NO: 41:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 77 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Tyr	Phe	His	Lys	Leu	Asn	Ile	Pro	Lys	Leu	Asp	Phe	Ser	Ser	Gln	Ala
1					5				10				15		

- 124 -

Asp	Leu	Arg	Asn	Glu	Ile	Lys	Thr	Leu	Leu	Lys	Ala	Gly	His	Ile	Ala
					20			25					30		
Trp	Thr	Ser	Ser	Gly	Lys	Gly	Ser	Trp	Lys	Trp	Ala	Cys	Pro	Arg	Phe
					35			40				45			
Ser	Asp	Glu	Gly	Thr	His	Glu	Ser	Gln	Ile	Ser	Phe	Thr	Ile	Glu	Gly
					50			55			60				
Pro	Leu	Thr	Ser	Phe	Gly	Leu	Ser	Asn	Lys	Ile	Asn	Ser			
					65			70			75				

(2) INFORMATION FOR SEQ ID NO: 42:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 99 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Trp	Tyr	Trp	Gly	Asp	Ile	Ser	Arg	Glu	Glu	Val	Asn	Glu	Lys	Leu	Arg
1					5			10				15			
Asp	Thr	Pro	Asp	Gly	Thr	Phe	Leu	Val	Arg	Asp	Ala	Ser	Ser	Lys	Ile
					20			25				30			
Gln	Gly	Asp	Tyr	Thr	Leu	Thr	Leu	Arg	Lys	Gly	Gly	Asn	Asn	Lys	Leu
					35			40			45				
Ile	Lys	Val	Phe	His	Arg	Asp	Gly	Lys	Tyr	Gly	Phe	Ser	Glu	Pro	Leu
					50			55			60				
Thr	Phe	Cys	Ser	Val	Val	Asp	Leu	Ile	Thr	His	Tyr	Arg	His	Glu	Ser
					65			70			75			80	
Leu	Ala	Gln	Tyr	Asn	Ala	Lys	Leu	Asp	Thr	Arg	Leu	Leu	Tyr	Pro	Val
					85			90				95			
Ser Lys Tyr															

(2) INFORMATION FOR SEQ ID NO: 43:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 100 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

- 125 -

Phe	Phe	Ser	Ala	Gln	Pro	Phe	Glu	Ile	Thr	Ala	Ser	Thr	Asn	Asn	Glu
1															15
				5											
Gly	Asn	Leu	Lys	Val	Arg	Phe	Pro	Leu	Arg	Leu	Thr	Gly	Lys	Ile	Asp
															30
				20											25
Phe	Leu	Asn	Asn	Tyr	Ala	Leu	Phe	Leu	Ser	Pro	Ser	Ala	Gln	Gln	Ala
															45
				35											40
Ser	Trp	Gln	Val	Ser	Ala	Arg	Phe	Asn	Gln	Tyr	Lys	Tyr	Asn	Gln	Asn
															50
				50											55
Phe	Ser	Ala	Gly	Asn	Asn	Glu	Asn	Ile	Met	Glu	Ala	His	Val	Gly	Ile
															65
				70											75
Asn	Gly	Glu	Ala	Asn	Leu	Asp	Phe	Leu	Asn	Ile	Pro	Leu	Thr	Ile	Pro
															85
															90
Glu	Met	Arg	Leu												
				100											

## (2) INFORMATION FOR SEQ ID NO: 44:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 106 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Trp	Phe	His	Gly	Lys	Leu	Gly	Ala	Gly	Arg	Asp	Gly	Arg	His	Ile	Ala
1															15
					5										
Glu	Arg	Leu	Leu	Thr	Glu	Tyr	Cys	Ile	Glu	Thr	Gly	Ala	Pro	Asp	Gly
															20
					20										25
Ser	Phe	Leu	Val	Arg	Glu	Ser	Glu	Thr	Phe	Val	Gly	Asp	Tyr	Thr	Leu
															35
															40
Ser	Phe	Trp	Arg	Asn	Gly	Lys	Val	Gln	His	Cys	Arg	Ile	His	Ser	Arg
															50
					55										60
Gln	Asp	Ala	Gly	Thr	Pro	Lys	Phe	Phe	Leu	Thr	Asp	Asn	Leu	Val	Phe
															65
					70										75
Asp	Ser	Leu	Tyr	Asp	Leu	Ile	Thr	His	Tyr	Gln	Gln	Val	Pro	Leu	Arg
															85
															90
Cys	Asn	Glu	Phe	Glu	Met	Arg	Leu	Ser	Glu						
															105

- 126 -

(2) INFORMATION FOR SEQ ID NO: 45:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 91 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met  
1 5 10 15

Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val  
20 25 30

His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile  
35 40 45

Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser  
50 55 60

Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val  
65 70 75 80

Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu  
85 90

(2) INFORMATION FOR SEQ ID NO: 46:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 203 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Val Ser Asp Gly Ile Ala Ala Leu Asp Leu Asn Ala Val Ala Asn Lys  
1 5 10 15

Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile Val Pro Glu Gln Thr Ile  
20 25 30

Glu Ile Pro Ser Ile Lys Phe Ser Val Pro Ala Gly Ile Val Ile Pro  
35 40 45

Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu Val Asp Ser Pro Val Tyr  
50 55 60

Asn Ala Thr Trp Ser Ala Ser Leu Lys Asn Lys Ala Asp Tyr Val Glu  
65 70 75 80

Thr Val Leu Asp Ser Thr Cys Ser Ser Thr Val Gln Phe Leu Glu Tyr  
85 90 95

- 127 -

Glu Leu Asn Val Leu Gly Thr His Lys Ile Glu Asp Gly Thr Leu Ala  
100 105 110

Ser Lys Thr Lys Gly Thr Leu Ala His Arg Asp Phe Ser Ala Glu Tyr  
115 120 125

Glu Glu Asp Gly Lys Phe Glu Gly Leu Gln Glu Trp Glu Gly Lys Ala  
130 135 140

His Leu Asn Ile Lys Ser Pro Ala Phe Thr Asp Leu His Leu Arg Tyr  
145 150 155 160

Gln Lys Asp Lys Lys Gly Ile Ser Thr Ser Ala Ala Ser Pro Ala Val  
165 170 175

Gly Thr Val Gly Met Asp Met Asp Glu Asp Asp Asp Phe Ser Lys Trp  
180 185 190

Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp  
195 200

(2) INFORMATION FOR SEQ ID NO: 47:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 214 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Leu Gly Gln Gly Cys Phe Gly Glu Val Trp Met Gly Thr Trp Asn Gly  
1 5 10 15

Thr Thr Arg Val Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser Pro  
20 25 30

Glu Ala Phe Leu Gln Glu Ala Gln Val Met Lys Lys Leu Arg His Glu  
35 40 45

Lys Leu Val Gln Leu Tyr Ala Val Val Ser Glu Glu Pro Ile Tyr Ile  
50 55 60

Val Thr Glu Tyr Met Ser Lys Gly Ser Leu Leu Asp Phe Leu Lys Gly  
65 70 75 80

Glu Thr Gly Lys Tyr Leu Arg Leu Pro Gln Leu Val Asp Met Ala Ala  
85 90 95

Gln Ile Ala Ser Gly Met Ala Tyr Val Glu Arg Met Asn Tyr Val His  
100 105 110

Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Gly Glu Asn Leu Val Cys  
115 120 125

- 128 -

Lys	Val	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Leu	Ile	Glu	Asp	Asn	Glu	Tyr
130						135					140				
Thr	Ala	Arg	Gln	Gly	Ala	Lys	Phe	Pro	Ile	Lys	Trp	Thr	Ala	Pro	Glu
145						150				155				160	
Ala	Ala	Leu	Tyr	Gly	Arg	Phe	Thr	Ile	Lys	Ser	Asp	Val	Trp	Ser	Phe
						165				170				175	
Gly	Ile	Leu	Leu	Thr	Glu	Leu	Thr	Thr	Lys	Gly	Arg	Val	Pro	Tyr	Pro
						180			185				190		
Gly	Met	Val	Asn	Arg	Glu	Val	Leu	Asp	Gln	Val	Glu	Arg	Gly	Tyr	Arg
						195			200				205		
Met	Pro	Cys	Pro	Pro	Glu										
						210									

(2) INFORMATION FOR SEQ ID NO: 48:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 213 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Leu	Gly	Asn	Gly	Gln	Phe	Gly	Glu	Val	Trp	Met	Gly	Thr	Trp	Asn	Gly
1								10						15	
Asn	Thr	Lys	Val	Ala	Ile	Lys	Thr	Leu	Lys	Pro	Gly	Thr	Met	Ser	Pro
					20			25					30		
Glu	Ser	Phe	Leu	Glu	Glu	Ala	Gln	Ile	Met	Lys	Lys	Leu	Lys	His	Asp
						35		40				45			
Lys	Leu	Val	Gln	Leu	Tyr	Ala	Val	Val	Ser	Glu	Glu	Pro	Ile	Tyr	Ile
						50		55			60				
Val	Thr	Glu	Tyr	Met	Asn	Lys	Gly	Ser	Leu	Leu	Asp	Phe	Leu	Lys	Asp
					65			70			75		80		
Gly	Glu	Gly	Arg	Ala	Leu	Lys	Leu	Pro	Asn	Leu	Val	Asp	Met	Ala	Ala
							85			90			95		
Gln	Val	Ala	Ala	Gly	Met	Ala	Tyr	Ile	Glu	Arg	Met	Asn	Tyr	Ile	His
						100			105			110			
Arg	Asp	Leu	Arg	Ser	Ala	Asn	Ile	Leu	Val	Gly	Asn	Gly	Leu	Ile	Cys
						115			120			125			
Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Leu	Ile	Glu	Asp	Asn	Glu	Tyr
						130			135			140			

- 129 -

Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu  
145 150 155 160

Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser Phe  
165 170 175

Gly Ile Leu Leu Thr Glu Leu Val Thr Lys Gly Arg Val Pro Tyr Pro  
180 185 190

Gly Met Asn Asn Arg Glu Val Leu Glu Gln Val Glu Arg Gly Tyr Arg  
195 200 205

Met Pro Cys Pro Gln  
210

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Ala Thr Tyr Asn Lys  
1 5 10 15

His Thr Lys Val Ala Val Lys Thr Met Lys Pro Gly Ser Met Ser Val  
20 25 30

Glu Ala Phe Leu Ala Glu Ala Asn Val Met Lys Thr Leu Gln His Asp  
35 40 45

Lys Leu Val Lys Leu His Ala Val Val Thr Lys Glu Pro Ile Tyr Ile  
50 55 60

Ile Thr Glu Phe Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser  
65 70 75 80

Asp Glu Gly Ser Lys Gln Pro Leu Pro Lys Leu Ile Asp Phe Ser Ala  
85 90 95

Gln Ile Ala Glu Gly Met Ala Phe Ile Glu Gln Arg Asn Tyr Ile His  
100 105 110

Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Ser Ala Ser Leu Val Cys  
115 120 125

Lys Ile Ala Asp Phe Gly Leu Ala Arg Val Ile Glu Asp Asn Glu Tyr  
130 135 140

Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu  
145 150 155 160

- 130 -

Ala	Ile	Asn	Phe	Gly	Ser	Phe	Thr	Ile	Lys	Ser	Asp	Val	Trp	Ser	Phe
														175	
									170						
															165
Gly	Ile	Leu	Leu	Met	Glu	Ile	Val	Thr	Tyr	Gly	Arg	Ile	Pro	Tyr	Pro
														190	
									185						180
Gly	Met	Ser	Asn	Pro	Glu	Val	Ile	Arg	Ala	Leu	Glu	Arg	Gly	Tyr	Arg
														205	
															195
															200
Met	Pro	Arg	Pro	Glu											
															210

(2) INFORMATION FOR SEQ ID NO: 50:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 218 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Leu	Gly	Ala	Gly	Gln	Phe	Gly	Glu	Val	Trp	Met	Gly	Tyr	Tyr	Asn	Asn
1										10					15

Ser	Thr	Lys	Val	Ala	Val	Lys	Thr	Leu	Lys	Pro	Gly	Thr	Met	Ser	Val
20								25						30	

Gln	Ala	Phe	Leu	Glu	Glu	Ala	Asn	Leu	Met	Lys	Thr	Leu	Gln	His	Asp
35								40					45		

Lys	Leu	Val	Arg	Leu	Tyr	Ala	Val	Val	Thr	Arg	Glu	Glu	Pro	Ile	Tyr
50								55					60		

Ile	Ile	Thr	Glu	Tyr	Met	Ala	Lys	Gly	Ser	Leu	Leu	Asp	Phe	Leu	Lys
65								70				75			80

Ser	Asp	Glu	Gly	Gly	Lys	Val	Leu	Leu	Pro	Lys	Leu	Ile	Asp	Phe	Ser
85								90				95			

Ala	Gln	Ile	Ala	Glu	Gly	Met	Ala	Tyr	Ile	Glu	Arg	Lys	Asn	Tyr	Ile
100								105				110			

His	Arg	Asp	Leu	Arg	Ala	Ala	Asn	Val	Leu	Val	Ser	Glu	Ser	Leu	Met
115								120				125			

Cys	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ile	Glu	Asp	Asn	Glu
130								135				140			

Tyr	Thr	Ala	Arg	Glu	Gly	Ala	Lys	Phe	Pro	Ile	Lys	Trp	Thr	Ala	Pro
145								150			155			160	

Glu	Ala	Ile	Asn	Phe	Gly	Cys	Phe	Thr	Ile	Lys	Ser	Asp	Val	Trp	Ser
165								170				175			

- 131 -

Phe Gly Ile Leu Leu Tyr Glu Ile Val Thr Tyr Gly Lys Ile Pro Tyr  
180 185 190

Pro Gly Arg Thr Asn Ala Asp Val Met Thr Ala Leu Ser Gln Gly Tyr  
195 200 205

Arg Met Pro Arg Val Glu Asn Cys Pro Asp  
210 215

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Gly Tyr Tyr Asn Gly  
1 5 10 15

His Thr Lys Val Ala Val Lys Ser Leu Lys Gln Gly Ser Met Ser Pro  
20 25 30

Asp Ala Phe Leu Ala Glu Ala Asn Leu Met Lys Gln Leu Gln His Gln  
35 40 45

Arg Leu Val Arg Leu Tyr Ala Val Val Thr Gln Glu Pro Ile Tyr Ile  
50 55 60

Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Val Asp Phe Leu Lys Thr  
65 70 75 80

Pro Ser Gly Ile Lys Leu Thr Ile Asn Lys Leu Leu Asp Met Ala Ala  
85 90 95

Gln Ile Ala Glu Gly Met Ala Phe Ile Glu Glu Arg Asn Tyr Ile His  
100 105 110

Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Ser Asp Thr Leu Ser Cys  
115 120 125

Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr  
130 135 140

Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu  
145 150 155 160

Ala Ile Asn Tyr Gly Thr Phe Thr Ile Lys Ser Asp Val Trp Ser Phe  
165 170 175

Gly Ile Leu Leu Thr Glu Ile Val Thr His Gly Arg Ile Pro Tyr Pro  
180 185 190

- 132 -

Gly Met Thr Asn Pro Glu Val Ile Gln Asn Leu Glu Arg Gly Tyr Arg  
195 200 205

Met Val Arg Pro Asp  
210

(2) INFORMATION FOR SEQ ID NO: 52:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 13 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Arg Lys Asn Tyr Ile His Arg Asp Leu Arg Ala Ala Asn  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 53:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 12 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Lys Gly Thr Leu Ala His Arg Asp Phe Ser Ala Glu  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 54:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 11 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Thr Lys Val Ala Val Lys Thr Leu Lys Pro Gly  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 55:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 11 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:

- 133 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Asp Lys Val Ala Ile Lys Thr Ile Arg Glu Gly  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 11 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Asp Leu Asn Ala Val Ala Asn Lys Ile Ala Asp  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Thr Ser Leu Arg Ala Pro Thr Met Pro Pro Pro Leu Pro Pro Val Pro  
1 5 10 15

Pro Gln Pro Ala Arg Arg Gln Ser Arg Arg Leu Pro Ala Ser Pro Val  
20 25 30

Ile Ser

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Ser Asp Ala Glu Gly Thr Ala Val Ala Pro Pro Thr Val Thr Pro Val  
1 5 10 15

- 134 -

Pro Ser Leu Glu Ala Pro Ser Glu Gln Ala Pro Thr Glu Gln Arg Pro  
20 25 30

Gly Val Gln Glu  
35

(2) INFORMATION FOR SEQ ID NO: 59:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 36 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Ser Asp Ala Glu Gly Thr Ala Val Ala Pro Pro Thr Ile Thr Pro Ile  
1 5 10 15

Pro Ser Leu Glu Ala Pro Ser Glu Gln Ala Pro Thr Glu Gln Arg Pro  
20 25 30

Gly Val Gln Glu  
35

(2) INFORMATION FOR SEQ ID NO: 60:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 36 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Ser Asp Ala Glu Trp Thr Ala Phe Val Pro Pro Asn Val Ile Leu Ala  
1 5 10 15

Pro Ser Leu Glu Ala Phe Phe Glu Gln Ala Leu Thr Glu Glu Thr Pro  
20 25 30

Gly Val Gln Asp  
35

(2) INFORMATION FOR SEQ ID NO: 61:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 36 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

- 135 -

Leu Val Thr Glu Ser Ser Val Leu Ala Thr Leu Thr Val Val Pro Asp  
1 5 10 15

Pro Ser Thr Glu Ala Ser Ser Glu Glu Ala Pro Thr Glu Gln Ser Pro  
20 25 30

Gly Val Gln Asp  
35

(2) INFORMATION FOR SEQ ID NO: 62:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 36 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Pro Val Met Glu Ser Thr Leu Leu Thr Thr Pro Thr Val Val Pro Val  
1 5 10 15

Pro Ser Thr Glu Leu Pro Ser Glu Glu Ala Pro Thr Glu Asn Ser Thr  
20 25 30

Gly Val Gln Asp  
35

(2) INFORMATION FOR SEQ ID NO: 63:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 36 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Pro Val Thr Glu Ser Ser Val Leu Thr Thr Pro Thr Val Ala Pro Val  
1 5 10 15

Pro Ser Thr Glu Ala Pro Ser Glu Gln Ala Pro Pro Glu Lys Ser Pro  
20 25 30

Val Val Gln Asp  
35

(2) INFORMATION FOR SEQ ID NO: 64:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 36 amino acids
  - (B) TYPE: amino acid

- 136 -

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Ser Glu Thr Glu Ser Gly Val Leu Glu Thr Pro Thr Val Val Pro Glu  
1 5 10 15

Pro Ser Met Glu Ala His Ser Glu Ala Ala Pro Thr Glu Gln Thr Pro  
20 25 30

Val Val Arg Gln  
35

(2) INFORMATION FOR SEQ ID NO: 65:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 27 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Ser Asp Thr Glu Ser Gly Thr Val Val Ala Pro Pro Thr Val Ile Gln  
1 5 10 15

Val Pro Ser Leu Gly Pro Pro Ser Glu Gln Asp  
20 25

(2) INFORMATION FOR SEQ ID NO: 66:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 37 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Pro Lys Asp Ala Thr Arg Phe Lys His Leu Arg Lys Tyr Thr Tyr Asn  
1 5 10 15

Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly Thr Ala Asp Ser Arg  
20 25 30

Ser Ala Thr Arg Ile  
35

(2) INFORMATION FOR SEQ ID NO: 67:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 34 amino acids

- 137 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Pro Lys Asp Ala Ser Gln Arg Arg Arg Ser Leu Glu Pro Ala Glu Asn  
1 5 10 15

Val His Gly Ala Gly Gly Ala Phe Pro Ala Ser Gln Thr Pro Ser  
20 25 30

Lys Pro

(2) INFORMATION FOR SEQ ID NO: 68:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 32 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Asp Lys Glu Ala Thr Lys Leu Thr Glu Glu Arg Asp Gly Ser Leu Asn  
1 5 10 15

Gln Ser Ser Gly Tyr Arg Tyr Gly Thr Asp Pro Thr Pro Gln His Tyr  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 69:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 39 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Ile Gln Asn Tyr His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu Lys  
1 5 10 15

Lys Leu Gln Ser Thr Thr Val Met Asn Pro Tyr Met Lys Leu Ala Pro  
20 25 30

Gly Glu Leu Thr Ile Ile Leu  
35

(2) INFORMATION FOR SEQ ID NO: 70:

- (i) SEQUENCE CHARACTERISTICS:

**SUBSTITUTE SHEET (RULE 26)**

- 138 -

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Pro	Glu	Glu	Arg	Pro	Thr	Phe	Glu	Tyr	Leu	Gln	Ala	Phe	Leu	Glu	Asp
1															15
Tyr	Phe	Thr	Ser	Thr	Glu	Pro	Gln	Tyr	Gln	Pro	Gly	Glu	Asn	Leu	
															30
20															

(2) INFORMATION FOR SEQ ID NO: 71:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Pro	Glu	Glu	Arg	Pro	Thr	Phe	Glu	Tyr	Leu	Gln	Ser	Phe	Leu	Glu	Asp
1															15
Tyr	Phe	Thr	Ala	Thr	Glu	Pro	Gln	Tyr	Gln	Pro	Gly	Glu	Asn	Leu	
															30
20															

(2) INFORMATION FOR SEQ ID NO: 72:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Pro	Glu	Glu	Arg	Pro	Thr	Phe	Glu	Tyr	Ile	Gln	Ser	Val	Leu	Asp	Asp
1															15
Phe	Tyr	Thr	Ala	Thr	Glu	Ser	Gln	Tyr	Gln	Gln	Gln	Pro			
20															25

(2) INFORMATION FOR SEQ ID NO: 73:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 29 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- 139 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Ala Glu Glu Arg Pro Thr Phe Asp Tyr Leu Gln Ser Val Leu Asp Asp  
1 5 10 15  
Phe Tyr Thr Ala Thr Glu Gly Gln Tyr Gln Gln Gln Pro  
20 25

(2) INFORMATION FOR SEQ ID NO: 74:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Pro Glu Asp Arg Pro Thr Phe Asp Tyr Leu Arg Ser Val Leu Glu Asp  
1 5 10 15  
Phe Phe Thr Ala Thr Glu Gly Gln Tyr Gln Pro Gln Pro  
20 25

(2) INFORMATION FOR SEQ ID NO: 75:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 6 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

Pro Xaa Xaa Xaa Xaa Pro  
1 5

(2) INFORMATION FOR SEQ ID NO: 76:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 40 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu Phe Ile Ile Pro  
1 5 10 15  
Thr Leu Asn Leu Asn Asp Phe Gln Val Pro Asp Leu His Ile Pro Glu  
20 25 30

- 140 -

Phe Gln Leu Pro His Ile Ser His  
35 40

(2) INFORMATION FOR SEQ ID NO: 77:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 22 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Pro Gln Asn Ala Lys Leu Lys Ile Lys Arg Pro Val Lys Val Gln Pro  
1 5 10 15

Ile Ala Arg Val Trp Tyr  
20

(2) INFORMATION FOR SEQ ID NO: 78:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 22 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu Phe Ile Ile Pro  
1 5 10 15

Thr Leu Asn Leu Asn Asp  
20

(2) INFORMATION FOR SEQ ID NO: 79:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 22 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Asn Asp Phe Gln Val Pro Asp Leu His Ile Pro Glu Phe Gln Leu Pro  
1 5 10 15

His Ile Ser His Thr Ile  
20

- 141 -

(2) INFORMATION FOR SEQ ID NO: 80:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 22 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

Pro	Ser	Leu	Glu	Leu	Pro	Val	Leu	His	Val	Pro	Arg	Asn	Leu	Lys	Leu
1															15
Ser Leu Pro His Phe Lys															
															20

(2) INFORMATION FOR SEQ ID NO: 81:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 379 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Met	Ala	Ser	Gly	Arg	Ala	Arg	Cys	Thr	Arg	Lys	Leu	Arg	Asn	Trp	Val
1															15
Val Glu Gln Val Glu Ser Gly Gln Phe Pro Gly Val Cys Trp Asp Asp															
															20 25 30
Thr Ala Lys Thr Met Phe Arg Ile Pro Trp Lys His Ala Gly Lys Gln															
															35 40 45
Asp Phe Arg Glu Ser Gln Asp Ala Ala Phe Phe Lys Ala Trp Ala Ile															
															50 55 60
Phe Lys Gly Lys Tyr Lys Glu Gly Asp Lys Glu Val Pro Glu Arg Gly															
															65 70 75 80
Arg Met Asp Val Ala Glu Pro Tyr Lys Val Tyr Gln Leu Leu Pro Pro															
															85 90 95
Gly Ile Val Ser Gly Gln Pro Gly Thr Gln Lys Val Pro Ser Lys Arg															
															100 105 110
Gln His Ser Ser Val Ser Ser Glu Arg Lys Glu Glu Asp Ala Met Gln															
															115 120 125
Asn Cys Thr Leu Ser Pro Ser Val Leu Gln Asp Ser Leu Asn Asn Glu															
															130 135 140
Glu Gly Ala Ser Gly Gly Ala Val His Ser Asp Ile Gly Ser Ser Ser															
															145 150 155 160

- 142 -

Ser	Ser	Ser	Ser	Pro	Glu	Pro	Gln	Glu	Val	Thr	Asp	Thr	Thr	Glu	Ala
				165			170			175					
Pro	Phe	Gln	Gly	Asp	Gln	Arg	Ser	Leu	Glu	Phe	Leu	Leu	Pro	Pro	Glu
	180				185				190						
Pro	Asp	Tyr	Ser	Leu	Leu	Leu	Thr	Phe	Ile	Tyr	Asn	Gly	Arg	Val	Val
	195				200				205						
Gly	Glu	Ala	Gln	Val	Gln	Ser	Leu	Asp	Cys	Arg	Leu	Val	Ala	Glu	Pro
	210			215				220							
Ser	Gly	Ser	Glu	Ser	Ser	Met	Glu	Gln	Val	Leu	Phe	Pro	Lys	Pro	Gly
	225			230		235			240						
Pro	Glu	Pro	Thr	Gln	Arg	Leu	Leu	Ser	Gln	Leu	Glu	Arg	Gly	Ile	Leu
	245				250			255							
Val	Ala	Ser	Asn	Pro	Arg	Gly	Leu	Phe	Val	Gln	Arg	Leu	Cys	Pro	Ile
	260			265			270								
Pro	Ile	Ser	Trp	Asn	Ala	Pro	Gln	Ala	Pro	Pro	Gly	Pro	Gly	Pro	His
	275			280			285								
Leu	Leu	Pro	Ser	Asn	Glu	Cys	Val	Glu	Leu	Phe	Arg	Thr	Ala	Tyr	Phe
	290			295			300								
Cys	Arg	Asp	Leu	Val	Arg	Tyr	Phe	Gln	Gly	Leu	Gly	Pro	Pro	Pro	Lys
	305			310		315			320						
Phe	Gln	Val	Thr	Leu	Asn	Phe	Trp	Glu	Glu	Ser	His	Gly	Ser	Ser	His
	325			330			335								
Thr	Pro	Gln	Asn	Leu	Ile	Thr	Val	Lys	Met	Glu	Gln	Ala	Phe	Ala	Arg
	340			345			350								
Tyr	Leu	Lys	Met	Glu	Gln	Ala	Phe	Ala	Arg	Tyr	Leu	Leu	Glu	Gln	Thr
	355			360			365								
Pro	Glu	Gln	Gln	Ala	Ala	Ile	Leu	Ser	Leu	Val					
	370			375											

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 383 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

Val	Ser	Leu	Val	Cys	Pro	Lys	Asp	Ala	Thr	Arg	Phe	Lys	His	Leu	Arg
1				5			10			15					

- 143 -

Lys	Tyr	Thr	Tyr	Asn	Tyr	Glu	Ala	Glu	Ser	Ser	Ser	Gly	Val	Pro	Gly
20								25					30		
Thr	Ala	Asp	Ser	Arg	Ser	Ala	Thr	Arg	Ile	Asn	Cys	Lys	Val	Glu	Leu
35								40				45			
Glu	Val	Pro	Gln	Leu	Cys	Ser	Phe	Ile	Leu	Lys	Thr	Ser	Gln	Cys	Thr
50								55			60				
Leu	Lys	Glu	Val	Tyr	Gly	Phe	Asn	Pro	Glu	Gly	Lys	Ala	Leu	Leu	Lys
65							70			75		80			
Lys	Thr	Lys	Asn	Ser	Glu	Glu	Phe	Ala	Ala	Ala	Met	Ser	Arg	Tyr	Glu
85								90			95				
Leu	Lys	Leu	Ala	Ile	Pro	Glu	Gly	Lys	Gln	Val	Phe	Leu	Tyr	Pro	Glu
100								105			110				
Lys	Asp	Glu	Pro	Thr	Tyr	Ile	Leu	Asn	Ile	Lys	Arg	Gly	Ile	Ile	Ser
115								120			125				
Ala	Leu	Leu	Val	Pro	Pro	Glu	Thr	Glu	Glu	Ala	Lys	Gln	Val	Leu	Phe
130								135			140				
Leu	Asp	Thr	Val	Tyr	Gly	Asn	Cys	Ser	Thr	His	Phe	Thr	Val	Lys	Thr
145							150			155		160			
Arg	Lys	Gly	Asn	Val	Ala	Thr	Glu	Ile	Ser	Thr	Glu	Arg	Asp	Leu	Gly
165								170			175				
Gln	Cys	Asp	Arg	Phe	Lys	Pro	Ile	Arg	Thr	Gly	Ile	Ser	Pro	Leu	Ala
180								185			190				
Leu	Ile	Lys	Gly	Met	Thr	Arg	Pro	Leu	Ser	Thr	Leu	Ile	Ser	Ser	Ser
195								200			205				
Gln	Ser	Cys	Gln	Tyr	Thr	Leu	Asp	Ala	Lys	Arg	Lys	His	Val	Ala	Glu
210								215			220				
Ala	Ile	Cys	Lys	Glu	Gln	His	Leu	Phe	Leu	Pro	Phe	Ser	Tyr	Lys	Asn
225								230			235		240		
Lys	Tyr	Gly	Met	Val	Ala	Gln	Val	Thr	Gln	Thr	Leu	Lys	Leu	Glu	Asp
245									250			255			
Thr	Pro	Lys	Ile	Asn	Ser	Arg	Phe	Phe	Gly	Glu	Gly	Thr	Lys	Lys	Met
260									265			270			
Gly	Leu	Ala	Phe	Glu	Ser	Thr	Lys	Ser	Thr	Ser	Pro	Pro	Lys	Gln	Ala
275								280			285				
Glu	Ala	Val	Leu	Lys	Thr	Leu	Gln	Glu	Leu	Lys	Lys	Leu	Thr	Ile	Ser
290								295			300				

- 144 -

Glu Gln Asn Ile Gln Arg Ala Asn Leu Phe Asn Lys Leu Val Thr Glu  
305 310 315 320

Leu Arg Gly Leu Ser Asp Glu Ala Val Thr Ser Leu Leu Pro Gln Leu  
325 330 335

Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu Val Gln Cys Gly  
340 345 350

Gln Pro Gln Cys Ser Thr His Ile Leu Lys Arg Val His Ala Asn Pro  
355 360 365

Leu Leu Ile Asp Val Val Thr Tyr Leu Val Ala Leu Ile Pro Glu  
370 375 380

(2) INFORMATION FOR SEQ ID NO: 83:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 394 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Phe Gly Leu Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln  
1 5 10 15

Asn Leu Val Tyr Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu Ile  
20 25 30

Gln Ser Gln Val Asp Ser Gln His Val Gly His Ser Val Leu Thr Ala  
35 40 45

Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg  
50 55 60

His Asp Ala His Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn Ser  
65 70 75 80

Leu Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn  
85 90 95

Glu Gly Asn Leu Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys Ile  
100 105 110

Asp Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln Gln  
115 120 125

Ala Ser Trp Gln Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn Gln  
130 135 140

Asn Phe Ser Ala Gly Asn Asn Glu Asn Ile Met Glu Ala His Val Gly  
145 150 155 160

- 145 -

Ile Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr Ile  
165 170 175

Pro Glu Met Arg Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys  
180 185 190

Asp Phe Ser Leu Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr  
195 200 205

Thr Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn  
210 215 220

Lys His Arg His Ser Ile Asn Pro Leu Ala Val Leu Cys Glu Phe Ile  
225 230 235 240

Ser Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn  
245 250 255

Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile Lys  
260 265 270

Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro Arg Thr  
275 280 285

Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu Val Ser  
290 295 300

Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro Lys Ala  
305 310 315 320

Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg Val Pro  
325 330 335

Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu His Val  
340 345 350

Pro Arg Asn Leu Lys Leu Ser Leu Pro His Phe Lys Glu Leu Cys Thr  
355 360 365

Ile Ser His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe  
370 375 380

Ser Phe Lys Ser Ser Val Ile Thr Leu Asn  
385 390

(2) INFORMATION FOR SEQ ID NO: 84:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 51 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

- 146 -

Met Ala Ser Gly Arg Ala Arg Cys Thr Arg Lys Leu Arg Asn Trp Val  
1 5 10 15

Val Glu Gln Val Glu Ser Gly Gln Phe Pro Gly Val Cys Trp Asp Asp  
20 25 30

Thr Ala Lys Thr Met Phe Arg Ile Pro Trp Lys His Ala Gly Lys Gln  
35 40 45

Asp Phe Arg  
50

(2) INFORMATION FOR SEQ ID NO: 85:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 48 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Pro Lys Asp Ala Thr Arg Phe Lys His Leu Arg Lys Tyr Thr Tyr Asn  
1 5 10 15

Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly Thr Ala Asp Ser Arg  
20 25 30

Ser Ala Thr Arg Ile Asn Cys Lys Val Glu Leu Glu Val Leu Pro Gln  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 86:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 37 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Pro Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe  
1 5 10 15

Ala Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly  
20 25 30

Lys Gln Val Phe Leu  
35

(2) INFORMATION FOR SEQ ID NO: 87:

- (i) SEQUENCE CHARACTERISTICS:

**SUBSTITUTE SHEET (RULE 26)**

- 147 -

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Cys	Ser	Thr	His	Phe	Thr	Val	Lys	Thr	Arg	Lys	Gly	Asn	Val	Ala	Thr
1				5				10							15
Glu	Ile	Ser	Thr	Glu	Arg	Asp	Leu	Gly	Gln	Cys	Asp	Arg	Phe	Lys	Pro
	20					25							30		
Ile	Arg	Thr	Gly	Ile	Ser										
	35														

(2) INFORMATION FOR SEQ ID NO: 88:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 51 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Cys	Ser	Thr	His	Ile	Leu	Gln	Trp	Leu	Lys	Arg	Val	His	Ala	Asn	Pro
1				5					10						15
Leu	Leu	Ile	Asp	Val	Val	Thr	Tyr	Leu	Val	Ala	Leu	Ile	Pro	Glu	Pro
	20					25						30			
Ser	Ala	Gln	Gln	Leu	Arg	Glu	Ile	Phe	Asn	Met	Ala	Arg	Asp	Gln	Arg
	35					40						45			
Ser	Arg	Ala													
	50														

(2) INFORMATION FOR SEQ ID NO: 89:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 38 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

His	Leu	Ser	Cys	Asp	Thr	Lys	Glu	Glu	Arg	Lys	Ile	Lys	Gly	Val	Ile
1				5				10							15
Ser	Ile	Pro	Arg	Leu	Gln	Ala	Glu	Ala	Arg	Ser	Glu	Ile	Leu	Ala	His
	20					25			30						

- 148 -

Trp Ser Pro Ala Lys Leu  
35

(2) INFORMATION FOR SEQ ID NO: 90:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 47 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Ser Val His Leu Asp Ser Lys Lys Lys Gln His Leu Phe Val Lys Glu  
1 5 10 15

Val Lys Ile Asp Gly Gln Phe Arg Val Ser Ser Phe Tyr Ala Lys Gly  
20 25 30

Thr Tyr Gly Leu Ser Cys Gln Arg Asp Pro Asn Thr Gly Arg Leu  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 91:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 40 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala Leu  
1 5 10 15

Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Ser Phe Asn Trp Glu  
20 25 30

Arg Gln Val Ser His Ala Lys Glu  
35 40

(2) INFORMATION FOR SEQ ID NO: 92:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 40 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Lys Leu Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp Ile  
1 5 10 15

- 149 -

Gln Ile Ala Leu Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu Ser  
20 25 30

Gln Leu Gln Thr Tyr Met Ile Gln  
35 40

(2) INFORMATION FOR SEQ ID NO: 93:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 50 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Glu Arg Ile Asn Asp Val Leu Glu His Val Lys His Phe Val Ile Asn  
1 5 10 15

Leu Ile Gly Asp Phe Glu Val Ala Glu Lys Ile Asn Ala Phe Arg Ala  
20 25 30

Lys Val His Glu Leu Ile Glu Arg Tyr Glu Val Asp Gln Gln Ile Gln  
35 40 45

Val Leu  
50

(2) INFORMATION FOR SEQ ID NO: 94:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 50 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu Lys Ser Phe Asp Tyr  
1 5 10 15

His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu Val Thr Gln  
20 25 30

Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro Gln Lys Ala Glu  
35 40 45

Ala Leu  
50

- 150 -

(2) INFORMATION FOR SEQ ID NO: 95:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 23 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln Asn Leu Val  
1 5 10 15

Tyr Glu Ser Gly Ser Leu Asn  
20

(2) INFORMATION FOR SEQ ID NO: 96:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 47 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Phe Ser Lys Leu Glu Ile Gln Ser Gln Val Asp Ser Gln His Val Gly  
1 5 10 15

His Ser Val Leu Thr Ala Lys Gly Met Ala Leu Phe Gly Glu Gly Gly  
20 25 30

Lys Ala Glu Phe Thr Gly Arg His Asp Ala His Leu Asn Gly Lys  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 97:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Val Lys Ala Gln Tyr Lys Lys Asn Lys His Arg His Ser Ile Thr Asn  
1 5 10 15

Pro Leu Ala Val Leu Cys Glu Phe Ile Ser Gln Ser Ile Lys Ser Phe  
20 25 30

Asp Arg His Phe Glu Lys Asn Arg Asn Asn Ala Leu Asp Phe Val Thr  
35 40 45

- 151 -

Lys Ser  
50

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu Lys Leu  
1 5 10 15

Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu Gly Ser His Asn  
20 25 30

Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val Ser Val Ala Lys  
35 40 45

Thr Thr Lys  
50

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val  
1 5 10 15

Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser  
20 25 30

Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys  
35 40 45

Leu Asn Asp  
50

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

- 152 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg Thr Ser Ser Phe Ala  
1                   5   15  
  
Leu Asn Leu Pro Thr Leu Pro Glu Val Lys Phe Pro Glu Val Asp Val  
20                   25   30  
  
Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile Pro Phe Phe Glu  
35                   40   45

Ile

(2) INFORMATION FOR SEQ ID NO: 101:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 48 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Leu His Leu Arg Tyr Gln Lys Asp Lys Lys Gly Ile Ser Thr Ser Ala  
1                   5   15  
  
Ala Ser Pro Ala Val Gly Thr Val Gly Met Asp Met Asp Glu Asp Asp  
20                   25   30  
  
Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp  
35                   40   45

(2) INFORMATION FOR SEQ ID NO: 102:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 48 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala  
1                   5   15  
  
Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val  
20                   25   30  
  
Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln Glu Trp  
35                   40   45

- 153 -

(2) INFORMATION FOR SEQ ID NO: 103:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 50 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Arg	Val	Thr	Gln	Lys	Phe	His	Met	Lys	Val	Lys	His	Leu	Ile	Asp	Ser
1				5					10					15	
Leu	Ile	Asp	Phe	Leu	Asn	Phe	Pro	Arg	Phe	Gln	Phe	Pro	Gly	Lys	Pro
							20		25				30		
Gly	Ile	Tyr	Thr	Arg	Glu	Glu	Leu	Cys	Thr	Met	Phe	Ile	Arg	Glu	Val
							35		40				45		
Gly	Thr														
	50														

(2) INFORMATION FOR SEQ ID NO: 104:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 48 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Trp	Lys	His	Ala	Gly	Lys	Gln	Asp	Phe	Arg	Glu	Ser	Gln	Asp	Ala	Ala
1					5				10				15		
Phe	Phe	Lys	Ala	Trp	Ala	Ile	Phe	Lys	Gly	Lys	Tyr	Lys	Glu	Gly	Asp
						20		25				30			
Lys	Glu	Val	Pro	Glu	Arg	Gly	Arg	Met	Asp	Val	Ala	Glu	Pro	Tyr	Lys
							35		40			45			

(2) INFORMATION FOR SEQ ID NO: 105:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 48 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Glu	His	Val	Lys	His	Phe	Val	Ile	Asn	Leu	Ile	Gly	Asp	Phe	Glu	Val
1					5				10			15			

- 154 -

Ala Glu Lys Ile Asn Ala Phe Arg Ala Lys Val His Glu Leu Ile Glu  
20 25 30

Arg Tyr Glu Val Asp Gln Gln Ile Gln Val Leu Met Asp Lys Leu Val  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 106:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 52 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Val Arg Lys Tyr Arg Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn  
1 5 10 15

Asp Tyr Leu Asn Ser Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys  
20 25 30

Glu Lys Leu Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp  
35 40 45

Ile Gln Ile Ala  
50

(2) INFORMATION FOR SEQ ID NO: 107:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 57 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu Lys Ile Ala Ile Ala  
1 5 10 15

Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys Ser Leu Asp Glu His  
20 25 30

Tyr His Ile Arg Val Asn Leu Val Lys Thr Ile His Asp Leu His Leu  
35 40 45

Phe Ile Glu Asn Ile Asp Phe Asn Lys  
50 55

- 155 -

(2) INFORMATION FOR SEQ ID NO: 108:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Lys Ile Thr Leu Ile Ile Asn Trp Leu Gln Glu Ala Leu Ser Ser Ala  
1 5 10 15

Ser Leu Ala His Met Lys Ala Lys Phe Arg Glu Thr Leu Glu Asp Thr  
20 25 30

Arg

(2) INFORMATION FOR SEQ ID NO: 109:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 32 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

Thr Asp His Phe Ser Leu Arg Ala Arg Tyr His Met Lys Ala Asp Ser  
1 5 10 15

Val Val Asp Leu Ser Tyr Asn Val Gln Gly Ser Gly Glu Thr Thr Tyr  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 110:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

Lys Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn Ala Lys Phe Ser  
1 5 10 15

Leu Asp Gly Lys  
20

- 156 -

(2) INFORMATION FOR SEQ ID NO: 111:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 52 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Asp Thr Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln  
1 5 10 15

Leu Lys Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys  
20 25 30

Leu Lys Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp Gln  
35 40 45

Leu Gly Thr Thr  
50

(2) INFORMATION FOR SEQ ID NO: 112:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 45 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Phe His Asp Phe Pro Asp Leu Gly Gln Glu Val Ala Leu Asn Ala Asn  
1 5 10 15

Thr Lys Asn Gln Lys Ile Arg Trp Lys Asn Glu Val Arg Ile His Ser  
20 25 30

Gly Ser Phe Gln Ser Gln Val Glu Leu Ser Asn Asp Gln  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 113:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 34 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His  
1 5 10 15

- 157 -

Met Lys Val Lys His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe  
20 25 30

Pro Arg

(2) INFORMATION FOR SEQ ID NO: 114:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 35 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly  
1 5 10 15

Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu Ile  
20 25 30

Ile Lys Ser  
35

(2) INFORMATION FOR SEQ ID NO: 115:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 211 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Glu Phe Thr Ile Val Ala Phe Val Lys Tyr Asp Lys Asn Gln Asp Val  
1 5 10 15

His Ser Ile Asn Leu Pro Phe Phe Glu Thr Leu Gln Glu Tyr Phe Glu  
20 25 30

Arg Asn Arg Gln Thr Ile Ile Val Val Leu Glu Asn Val Gln Arg Lys  
35 40 45

Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala  
50 55 60

Leu Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser Phe Asn  
65 70 75 80

Trp Glu Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr  
85 90 95

- 158 -

Lys	Lys	Tyr	Arg	Ile	Thr	Glu	Asn	Asp	Ile	Gln	Ile	Ala	Leu	Asp	Asp
				100			105					110			
Ala	Lys	Ile	Asn	Phe	Asn	Glu	Lys	Leu	Ser	Gln	Leu	Gln	Thr	Tyr	Met
				115			120					125			
Ile	Gln	Phe	Asp	Gln	Tyr	Ile	Lys	Asp	Ser	Tyr	Asp	Leu	His	Asp	Leu
				130			135					140			
Lys	Ile	Ala	Ile	Ala	Asn	Ile	Ile	Asp	Glu	Ile	Ile	Glu	Lys	Leu	Lys
				145			150					155			160
Ser	Leu	Asp	Glu	His	Tyr	His	Ile	Arg	Val	Ile	Leu	Val	Lys	Thr	Ile
				165				170					175		
His	Asp	Leu	His	Leu	Phe	Ile	Glu	Asn	Ile	Asp	Phe	Asn	Lys	Ser	Gly
				180			185					190			
Ser	Ser	Thr	Ala	Ser	Trp	Ile	Gln	Asn	Val	Asp	Thr	Lys	Tyr	Gln	Ile
				195			200					205			
Arg	Ile	Gln													
		210													

(2) INFORMATION FOR SEQ ID NO: 116:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 174 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

Gly	Pro	Leu	Pro	Thr	Leu	Val	Ser	Gly	Gly	Thr	Ile	Leu	Ala	Thr	Val
1					5				10				15		
Pro	Leu	Val	Val	Asp	Ala	Glu	Lys	Leu	Pro	Ile	Asn	Arg	Leu	Ala	Ala
				20				25				30			
Gly	Ser	Lys	Ala	Pro	Ala	Ser	Ala	Gln	Ser	Arg	Gly	Glu	Lys	Arg	Thr
				35				40				45			
Ala	His	Asn	Ala	Ile	Glu	Lys	Arg	Tyr	Arg	Ser	Ser	Ile	Asn	Asp	Lys
				50				55				60			
Ile	Ile	Glu	Leu	Lys	Asp	Leu	Val	Val	Gly	Thr	Glu	Ala	Lys	Leu	Asn
				65				70				75			80
Lys	Ser	Ala	Val	Leu	Arg	Lys	Ala	Ile	Asp	Tyr	Ile	Arg	Phe	Leu	Gln
				85					90				95		
His	Ser	Asn	Gln	Lys	Leu	Lys	Gln	Glu	Asn	Leu	Ser	Leu	Arg	Thr	Ala
				100				105				110			

- 159 -

Val His Lys Ser Lys Ser Leu Lys Asp Leu Val Ser Ala Cys Gly Ser  
115 120 125

Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val Lys Thr Glu Val Glu  
130 135 140

Asp Thr Leu Thr Pro Pro Pro Ser Asp Ala Gly Ser Pro Phe Gln Ser  
145 150 155 160

Ser Pro Leu Ser Leu Gly Ser Arg Gly Ser Gly Ser Gly Gly  
165 170

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 172 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Gln Val Pro Thr Leu Val Gly Ser Ser Gly Thr Ile Leu Thr Thr Met  
1 5 10 15

Pro Val Met Met Gly Gln Glu Lys Val Pro Ile Lys Gln Val Pro Gly  
20 25 30

Gly Val Lys Gln Leu Glu Pro Pro Lys Glu Gly Glu Arg Arg Thr Thr  
35 40 45

His Asn Ile Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile  
50 55 60

Ile Glu Leu Lys Asp Leu Val Met Gly Thr Asp Ala Lys Met His Lys  
65 70 75 80

Ser Gly Val Leu Arg Lys Ala Ile Asp Tyr Ile Lys Tyr Leu Gln Gln  
85 90 95

Val Asn His Lys Leu Arg Gln Glu Asn Met Val Leu Lys Leu Ala Asn  
100 105 110

Gln Lys Asn Lys Leu Leu Lys Gly Ile Asp Leu Gly Ser Leu Val Asp  
115 120 125

Asn Glu Val Asp Leu Lys Ile Glu Asp Phe Asn Gln Asn Val Leu Leu  
130 135 140

Met Ser Pro Pro Ala Ser Asp Ser Gly Ser Gln Ala Gly Phe Ser Pro  
145 150 155 160

Tyr Ser Ile Asp Ser Glu Pro Gly Ser Pro Leu Leu  
165 170

- 160 -

(2) INFORMATION FOR SEQ ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 173 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

Gly Pro Leu Gln Thr Leu Val Ser Gly Gly Thr Ile Leu Ala Thr Val  
1 5 10 15

Pro Leu Val Val Asp Thr Asp Lys Leu Pro Ile His Arg Leu Ala Ala  
20 25 30

Gly Gly Lys Ala Leu Gly Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr  
35 40 45

Ala His Asn Ala Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys  
50 55 60

Ile Val Glu Leu Lys Asp Leu Val Val Gly Thr Glu Ala Lys Leu Asn  
65 70 75 80

Lys Ser Ala Val Leu Arg Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln  
85 90 95

His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu Thr Leu Arg Ser Ala  
100 105 110

His Lys Ser Lys Ser Leu Lys Asp Leu Val Ser Ala Cys Gly Ser Gly  
115 120 125

Gly Gly Thr Asp Val Ser Met Glu Gly Met Lys Pro Glu Val Val Glu  
130 135 140

Thr Leu Thr Pro Pro Pro Ser Asp Ala Gly Ser Pro Ser Gln Ser Ser  
145 150 155 160

Pro Leu Ser Leu Gly Ser Arg Gly Ser Ser Ser Gly Gly  
165 170

(2) INFORMATION FOR SEQ ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 243 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

- 161 -

Asp Glu Pro Pro Gln Ser Pro Trp Asp Arg Val Lys Asp Leu Ala Thr  
1 5 10 15

Val Tyr Val Asp Val Leu Lys Asp Ser Gly Arg Asp Tyr Val Ser Gln  
20 25 30

Phe Glu Gly Ser Ala Leu Gly Lys Gln Leu Asn Leu Lys Leu Leu Asp  
35 40 45

Asn Trp Asp Ser Val Thr Ser Thr Phe Ser Lys Leu Arg Glu Gln Leu  
50 55 60

Gly Pro Val Thr Gln Glu Phe Trp Asp Asn Leu Glu Lys Glu Thr Glu  
65 70 75 80

Gly Leu Arg Gln Glu Met Ser Lys Asp Leu Glu Glu Val Lys Ala Lys  
85 90 95

Val Gln Pro Tyr Leu Asp Asp Phe Gln Lys Lys Trp Gln Glu Glu Met  
100 105 110

Glu Leu Tyr Arg Gln Lys Val Glu Pro Leu Arg Ala Glu Leu Gln Glu  
115 120 125

Gly Ala Arg Gln Lys Leu His Glu Leu Gln Glu Lys Leu Ser Pro Leu  
130 135 140

Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg  
145 150 155 160

Thr His Leu Ala Pro Tyr Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala  
165 170 175

Arg Leu Glu Ala Leu Lys Glu Asn Gly Gly Ala Arg Leu Ala Glu Tyr  
180 185 190

His Ala Lys Ala Thr Glu His Leu Ser Thr Leu Ser Glu Lys Ala Lys  
195 200 205

Pro Ala Leu Glu Asp Leu Arg Gln Gly Leu Leu Pro Val Leu Glu Ser  
210 215 220

Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu  
225 230 235 240

Asn Thr Gln

(2) INFORMATION FOR SEQ ID NO: 120:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 268 amino acids
  - (B) TYPE: amino acid

- 162 -

(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

Gln Gln Val Pro Val Leu Leu Gln Pro His Phe Ile Lys Ala Asp Ser  
1 5 10 15

Leu Leu Leu Thr Ala Met Lys Thr Asp Gly Ala Thr Val Lys Ala Ala  
20 25 30

Gly Leu Ser Pro Leu Val Ser Gly Thr Thr Val Gln Thr Gly Pro Leu  
35 40 45

Pro Thr Leu Val Ser Gly Gly Thr Ile Leu Ala Thr Val Pro Leu Val  
50 55 60

Val Asp Ala Glu Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys  
65 70 75 80

Ala Pro Ala Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn  
85 90 95

Ala Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu  
100 105 110

Leu Lys Asp Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser Ala  
115 120 125

Val Leu Arg Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln His Ser Asn  
130 135 140

Gln Lys Leu Lys Gln Glu Asn Leu Ser Leu Arg Thr Ala Val His Lys  
145 150 155 160

Ser Lys Ser Leu Lys Asp Leu Val Ser Ala Cys Gly Ser Gly Gly Asn  
165 170 175

Thr Asp Val Leu Met Glu Gly Val Lys Thr Glu Val Glu Asp Thr Leu  
180 185 190

Thr Pro Pro Pro Ser Asp Ala Gly Ser Pro Phe Gln Ser Ser Pro Leu  
195 200 205

Ser Leu Gly Ser Arg Gly Ser Gly Ser Gly Ser Gly Ser Asp Ser  
210 215 220

Glu Pro Asp Ser Pro Val Phe Glu Asp Ser Lys Ala Lys Pro Glu Gln  
225 230 235 240

Arg Pro Ser Leu His Ser Arg Gly Met Leu Asp Arg Ser Arg Leu Ala  
245 250 255

Leu Cys Thr Leu Val Phe Leu Cys Leu Ser Cys Asn  
260 265

- 163 -

(2) INFORMATION FOR SEQ ID NO: 121:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 77 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

Gln Ala Lys Glu Pro Cys Val Glu Ser Leu Val Ser Gln Tyr Phe Gln  
1 5 10 15

Thr Val Thr Asp Tyr Gly Lys Asp Leu Met Glu Lys Val Lys Ser Pro  
20 25 30

Glu Leu Gln Ala Glu Ala Lys Ser Tyr Phe Glu Lys Ser Lys Glu Gln  
35 40 45

Leu Thr Pro Leu Ile Lys Lys Ala Gly Thr Glu Leu Val Asn Phe Leu  
50 55 60

Ser Tyr Phe Val Glu Leu Gly Thr Gln Pro Ala Thr Gln  
65 70 75

(2) INFORMATION FOR SEQ ID NO: 122:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 71 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

Glu Ala Lys Leu Asn Lys Ser Ala Val Leu Arg Lys Ala Ile Asp Tyr  
1 5 10 15

Ile Arg Phe Leu Gln His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu  
20 25 30

Ser Leu Arg Thr Ala Val His Lys Ser Lys Ser Leu Lys Asp Leu Val  
35 40 45

Ser Ala Cys Gly Ser Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val  
50 55 60

Lys Thr Glu Val Glu Asp Thr  
65 70

(2) INFORMATION FOR SEQ ID NO: 123:

- (i) SEQUENCE CHARACTERISTICS:

**SUBSTITUTE SHEET (RULE 26)**

- 164 -

- (A) LENGTH: 397 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp Lys  
1 5 10 15

Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu Val  
20 25 30

Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu Lys  
35 40 45

Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Leu Arg Ala Arg Leu  
50 55 60

Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu Arg  
65 70 75 80

Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr Gln  
85 90 95

Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu Ala  
100 105 110

Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln Ala  
115 120 125

Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln Asn  
130 135 140

Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe Lys  
145 150 155 160

Val Lys Ile Asp Gln Thr Val Glu Leu Arg Arg Ser Leu Ala Pro  
165 170 175

Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly Leu  
180 185 190

Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile Ser  
195 200 205

Ala Ser Ala Glu Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu  
210 215 220

Ala Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu  
225 230 235 240

Gly Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg  
245 250 255

- 165 -

Ile Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala			
260	265	270	
Glu Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys			
275	280	285	
Ser Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe			
290	295	300	
Arg Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val			
305	310	315	320
Gln Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp			
325	330	335	
Val Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val			
340	345	350	
Asn Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr			
355	360	365	
Leu Ser Leu Pro Glu Leu Glu Gln Gln Glu Gln Gln Gln Glu Gln			
370	375	380	
Gln Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser			
385	390	395	

(2) INFORMATION FOR SEQ ID NO: 124:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 422 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

Glu Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala			
1	5	10	15
Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn Ala Ile Glu			
20	25	30	
Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu Leu Lys Asp			
35	40	45	
Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser Ala Val Leu Arg			
50	55	60	
Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln His Ser Asn Gln Lys Leu			
65	70	75	80
Lys Gln Glu Asn Leu Ser Leu Arg Thr Ala Val His Lys Ser Lys Ser			
85	90	95	

- 166 -

Leu Lys Asp Leu Val Ser Ala Cys Gly Ser Gly Gly Asn Thr Asp Val  
100 105 110

Leu Met Glu Gly Val Lys Thr Glu Val Glu Asp Thr Leu Thr Pro Pro  
115 120 125

Pro Arg Asp Ala Gly Ser Pro Phe Gln Ser Ser Pro Leu Ser Leu Gly  
130 135 140

Ser Arg Gly Ser Gly Ser Gly Ser Gly Ser Asp Ser Glu Pro Asp  
145 150 155 160

Ser Pro Val Phe Glu Asp Ser Lys Ala Lys Pro Glu Gln Arg Pro Ser  
165 170 175

Leu His Ser Arg Gly Met Leu Asp Arg Ser Arg Leu Ala Leu Cys Thr  
180 185 190

Leu Val Phe Leu Cys Leu Ser Cys Asn Pro Leu Ala Ser Leu Leu Gly  
195 200 205

Ala Arg Gly Leu Pro Ser Pro Ser Asp Thr Thr Ser Val Tyr His Ser  
210 215 220

Pro Gly Arg Asn Val Leu Gly Thr Glu Ser Arg Asp Gly Pro Gly Trp  
225 230 235 240

Ala Gln Ala Val Gln Leu Phe Leu Cys Asp Leu Leu Leu Val Val Arg  
245 250 255

Thr Ser Leu Trp Arg Gln Gln Pro Pro Ala Pro Ala Pro Ala Ala  
260 265 270

Gln Gly Ala Ser Ser Arg Pro Gln Ala Ser Ala Leu Glu Ile Arg Gly  
275 280 285

Phe Gln Arg Asp Leu Ser Ser Leu Arg Arg Leu Ala Gln Ser Phe Arg  
290 295 300

Pro Ala Met Arg Arg Val Phe Leu His Glu Ala Thr Ala Arg Leu Met  
305 310 315 320

Ala Gly Ala Ser Pro Thr Arg Thr His Gln Leu Leu Asp Arg Ser Leu  
325 330 335

Arg Arg Arg Ala Gly Pro Gly Gly Lys Gly Gly Ala Val Ala Glu Leu  
340 345 350

Glu Pro Arg Pro Thr Arg Arg Glu His Ala Glu Ala Leu Leu Ala  
355 360 365

Ser Cys Tyr Leu Pro Pro Gly Phe Leu Ser Ala Pro Gly Gln Arg Val  
370 375 380

Gly Met Leu Ala Glu Ala Ala Arg Thr Leu Glu Lys Leu Gly Asp Arg  
385 390 395 400

- 167 -

Arg Leu Leu His Asp Cys Gln Gln Met Leu Met Arg Leu Gly Gly Gly  
405 410 415

Thr Thr Val Thr Ser Ser  
420

(2) INFORMATION FOR SEQ ID NO: 125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 142 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

Glu Lys Met Ser Leu Arg Asn Arg Leu Ser Lys Ser Arg Glu Asn Pro  
1 5 10 15

Glu Glu Asp Glu Asp Gln Arg Asn Pro Ala Lys Glu Ser Leu Glu Thr  
20 25 30

Pro Ser Asn Gly Arg Ile Asp Ile Lys Gln Leu Ile Ala Lys Lys Ile  
35 40 45

Lys Leu Thr Ala Asn Gly Arg Ile Asp Ile Lys Gln Leu Ile Ala Lys  
50 55 60

Lys Ile Lys Leu Thr Ala Glu Asn Gly Arg Ile Asp Ile Lys Gln Leu  
65 70 75 80

Ile Ala Lys Ile Lys Leu Thr Ala Glu Ala Glu Glu Leu Lys Pro  
85 90 95

Phe Phe Met Lys Glu Val Gly Ser His Phe Asp Asp Phe Val Thr Asn  
100 105 110

Leu Ile Glu Lys Ser Ala Ser Leu Asp Asn Lys Ala His Ser Phe Val  
115 120 125

Arg Glu Asn Val Pro Arg Val Leu Asn Ser Ala Lys Glu Lys  
130 135 140

(2) INFORMATION FOR SEQ ID NO: 126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 135 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

- 168 -

Glu	Lys	Leu	Pro	Ile	Asn	Arg	Leu	Ala	Ala	Gly	Ser	Lys	Ala	Pro	Ala
1															15
Ser	Ala	Gln	Ser	Arg	Gly	Glu	Lys	Arg	Thr	Ala	His	Asn	Ala	Ile	Glu
															30
Lys	Arg	Tyr	Arg	Ser	Ser	Ile	Asn	Asp	Lys	Ile	Ile	Glu	Leu	Lys	Asp
															45
Leu	Val	Val	Gly	Thr	Glu	Ala	Lys	Leu	Asn	Lys	Ser	Tyr	Ile	Arg	Phe
															60
Leu	Gln	His	Ser	Asn	Gln	Lys	Leu	Lys	Gln	Glu	Asn	Leu	Ser	Leu	Arg
65															80
Thr	Ala	Val	His	Lys	Ser	Ser	Leu	Lys	Asp	Leu	Val	Ser	Ala	Cys	
															95
Gly	Ser	Gly	Gly	Asn	Thr	Asp	Val	Leu	Met	Glu	Gly	Val	Lys	Thr	Glu
															110
Val	Glu	Asp	Lys	Ala	Lys	Pro	Glu	Gln	Arg	Pro	Ser	Leu	His	Ser	Arg
															125
Gly	Met	Leu	Asp	Arg	Ser	Arg									
															135

(2) INFORMATION FOR SEQ ID NO: 127:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Arg	Arg	His	Cys	Pro	Leu	Lys	Asn	Pro	Thr	Phe	Leu	Asp	Tyr	Val	Arg
1															15
Pro	Arg	Ser	Trp	Thr	Cys	Arg	Tyr	Val	Phe						
															25

(2) INFORMATION FOR SEQ ID NO: 128:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 25 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

- 169 -

Arg Arg Arg Ala Gly Pro Gly Gly Lys Gly Ala Val Ala Glu Leu  
1 5 10 15

Glu Pro Arg Pro Thr Arg Arg Glu His  
20 25

(2) INFORMATION FOR SEQ ID NO: 129:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 114 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Ala Met Leu Gly Gln Ser Thr Glu Glu Leu Arg Val Arg Leu Ala Ser  
1 5 10 15

His Leu Arg Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu  
20 25 30

Gln Lys Arg Leu Ala Val Tyr Gln Ala Gly Ala Arg Glu Gly Ala Glu  
35 40 45

Arg Gly Leu Ser Ala Ile Arg Glu Arg Leu Gly Pro Leu Val Glu Gln  
50 55 60

Gly Arg Val Arg Ala Ala Thr Val Gly Ser Leu Ala Gly Gln Pro Leu  
65 70 75 80

Gln Glu Arg Ala Gln Ala Trp Gly Glu Arg Leu Arg Ala Arg Met Glu  
85 90 95

Glu Met Gly Ser Arg Thr Arg Asp Arg Leu Asp Glu Val Lys Glu Gln  
100 105 110

Val Ala

(2) INFORMATION FOR SEQ ID NO: 130:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 107 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala Ser  
1 5 10 15

- 170 -

Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn Ala Ile Glu Lys  
20 25 30

Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu Leu Lys Asp Leu  
35 40 45

Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser Ala Val Leu Arg Lys  
50 55 60

Ala Ile Asp Tyr Ile Arg Phe Leu Gln His Ser Asn Gln Lys Leu Lys  
65 70 75 80

Gln Glu Asn Leu Ser Leu Arg Thr Ala Val His Lys Ser Lys Ser Leu  
85 90 95

Lys Asp Leu Val Ser Ala Cys Gly Ser Gly Gly  
100 105

(2) INFORMATION FOR SEQ ID NO: 131:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 42 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

Thr Gln Gln Pro Gln Gln Asp Glu Met Pro Ser Pro Thr Phe Leu Thr  
1 5 10 15

Gln Val Lys Glu Ser Leu Ser Ser Tyr Trp Glu Ser Ala Lys Thr Ala  
20 25 30

Ala Gln Asn Leu Tyr Glu Lys Thr Tyr Leu  
35 40

(2) INFORMATION FOR SEQ ID NO: 132:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 45 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

Ser Gln Ile Gln Gln Val Pro Val Leu Leu Gln Pro His Phe Ile Lys  
1 5 10 15

Ala Asp Ser Leu Leu Leu Thr Ala Met Lys Thr Asp Gly Ala Thr Val  
20 25 30

- 171 -

Lys Ala Ala Gly Leu Ser Pro Leu Val Ser Gly Thr Thr  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 133:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 45 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

Ser Leu Leu Ser Phe Met Gln Gly Tyr Met Lys His Ala Thr Lys Thr  
1 5 10 15

Ala Lys Asp Ala Leu Ser Ser Val Gln Glu Ser Gln Val Ala Gln Gln  
20 25 30

Ala Arg Gly Trp Val Thr Asp Gly Phe Ser Ser Leu Lys  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 134:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 47 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

Ala Pro Ala Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn  
1 5 10 15

Ala Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu  
20 25 30

Leu Lys Asp Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser  
35 40 45

(2) INFORMATION FOR SEQ ID NO: 135:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 28 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Asp Tyr Trp Ser Thr Val Lys Asp Lys Phe Ser Glu Phe Trp Asp Leu  
1 5 10 15

- 172 -

Asp Pro Glu Val Arg Pro Thr Ser Ala Val Ala Ala  
20 25

(2) INFORMATION FOR SEQ ID NO: 136:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 32 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

Glu Ile Tyr Val Ala Ala Ala Leu Arg Val Lys Thr Ser Leu Pro Arg  
1 5 10 15

Ala Leu His Phe Leu Thr Arg Phe Phe Leu Ser Ser Ala Arg Gln Ala  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 137:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 5 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Glu Lys Ile Pro Thr  
1 5

(2) INFORMATION FOR SEQ ID NO: 138:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 5 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

Glu Lys Leu Pro Ile  
1 5

(2) INFORMATION FOR SEQ ID NO: 139:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:

- 173 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

Glu Asn Gly Arg Cys Ile Gln Ala Asn Tyr Ser Leu Met Glu Asn Gly  
1 5 10 15  
  
Lys Ile Lys Val Leu Asn Gln Glu Leu Arg Ala Asp Gly  
20 25

(2) INFORMATION FOR SEQ ID NO: 140:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

Ala Val Leu Arg Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln His Ser  
1 5 10 15  
  
Asn Gln Lys Leu Lys Gln Glu Asn Leu Ser Leu Arg Thr Ala Val  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 141:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

Met Lys Gln Leu Glu Asp Lys Val Glu Glu Leu Leu Ser Lys Asn Tyr  
1 5 10 15  
  
His Leu Glu Asn Glu Val Ala Arg Leu Lys Lys Leu Val Gly Glu Arg  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 142:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

- 174 -

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

Arg	Ile	Gln	Ile	Gln	Glu	Lys	Leu	Gln	Gln	Leu	Lys	Arg	His	Ile	Gln
1				5								15			
Asn	Ile	Asp	Ile	Gln	His	Leu	Ala	Gly	Lys	Leu	Lys	Gln	His	Ile	Glu
			20					25				30			

(2) INFORMATION FOR SEQ ID NO: 145:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 35 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

Val	Leu	Gln	Gln	Val	Lys	Ile	Lys	Asp	Tyr	Phe	Glu	Lys	Leu	Val	Gly
1				5								10		15	
Phe	Ile	Asp	Asp	Ala	Val	Lys	Lys	Leu	Asn	Glu	Leu	Ser	Phe	Lys	Thr
		20				25						30			
Phe	Ile	Glu													
		35													

(2) INFORMATION FOR SEQ ID NO: 146:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

Glu	Leu	Ser	Phe	Lys	Thr	Phe	Ile	Glu	Asp	Val	Asn	Lys	Phe	Leu	Asp
1				5				10				15			
Met	Leu	Ile	Lys	Lys	Leu	Lys	Ser	Phe	Asp	Tyr	His	Gln	Phe	Val	
			20				25				30				

(2) INFORMATION FOR SEQ ID NO: 147:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 amino acids
  - (B) TYPE: amino acid

- 175 -

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

His	Gln	Phe	Val	Asp	Glu	Thr	Asn	Asp	Lys	Ile	Arg	Glu	Val	Thr	Gln
1				5					10					15	
Arg	Leu	Asn	Gly	Glu	Ile	Gln	Ala	Leu	Glu	Leu	Pro				
		20						25							

(2) INFORMATION FOR SEQ ID NO: 148:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:

Ala	Ala	Lys	Asn	Leu	Thr	Asp	Phe	Ala	Glu	Gln	Tyr	Ser	Ile	Gln	Asp
1				5				10					15		
Trp	Ala	Lys	Arg	Met	Lys	Ala	Leu	Val	Glu	Gln	Gly	Phe	Thr	Val	
			20				25					30			

(2) INFORMATION FOR SEQ ID NO: 149:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 35 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

Ser	Ala	Ser	Leu	Ala	His	Met	Lys	Ala	Lys	Phe	Arg	Glu	Thr	Leu	Glu
1					5				10				15		
Asp	Thr	Arg	Asp	Arg	Met	Tyr	Asp	Met	Asp	Ile	Gln	Gln	Glu	Leu	Gln
		20					25				30				
Arg	Tyr	Leu													
		35													

(2) INFORMATION FOR SEQ ID NO: 150:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 35 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- 176 -

(2) INFORMATION FOR SEQ ID NO: 149:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 35 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

Ser	Ala	Ser	Leu	Ala	His	Met	Lys	Ala	Phe	Arg	Glu	Thr	Leu	Glu	
1														15	
Asp	Thr	Arg	Asp	Arg	Met	Tyr	Asp	Met	Asp	Ile	Gln	Gln	Glu	Leu	Gln
														30	
Arg	Tyr	Leu													
		35													

(2) INFORMATION FOR SEQ ID NO: 150:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 35 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

Cys	Leu	Asn	Leu	His	Lys	Phe	Asn	Glu	Phe	Ile	Gln	Asn	Glu	Leu	Gln
1														15	
Glu	Ala	Ser	Gln	Glu	Leu	Gln	Gln	Ile	His	Gln	Tyr	Ile	Met	Ala	Leu
														30	
Arg	Glu	Glu													
		35													

(2) INFORMATION FOR SEQ ID NO: 151:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

Phe	Leu	Ile	Tyr	Ile	Thr	Glu	Leu	Leu	Lys	Lys	Leu	Gln	Ser	Thr	Thr
1														15	
Val	Met	Asn	Pro	Tyr	Met	Lys	Leu	Ala	Pro	Gly	Glu	Leu	Thr	Ile	Ile
														30	

- 177 -

(2) INFORMATION FOR SEQ ID NO: 152:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

Arg	Leu	Leu	Asp	His	Arg	Val	Pro	Glu	Thr	Asp	Met	Thr	Phe	Arg	His
1					5						10			15	
Val	Gly	Ser	Lys	Leu	Ile	Val	Ala	Met	Ser	Ser	Trp	Leu	Gln		
					20			25				30			

(2) INFORMATION FOR SEQ ID NO: 153:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

Leu	Asn	Phe	Ser	Lys	Leu	Glu	Ile	Gln	Ser	Gln	Val	Asp	Ser	Gln	His
1					5				10					15	
Val	Gly	His	Ser	Val	Leu	Thr	Ala	Lys	Gly	Met	Ala	Leu	Phe		
					20			25			30				

(2) INFORMATION FOR SEQ ID NO: 154:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

Asn	Gln	Asn	Phe	Ser	Ala	Gly	Asn	Asn	Glu	Asn	Ile	Met	Glu	Ala	His
1							5		10				15		
Val	Gly	Ile	Asn	Gly	Glu	Ala	Asn	Leu	Asp	Phe	Leu	Asn	Ile		
						20			25			30			

- 178 -

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 29 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

Met	Val	Val	Thr	Arg	Ile	Ala	Pro	Ser	Pro	Thr	Gly	Asp	Pro	His	Val
1				5						10				15	
Gly Thr Ala Tyr Ile Ala Leu Phe Asn Tyr Ala Trp Ala															
20 25															

(2) INFORMATION FOR SEQ ID NO: 156:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

Thr	Thr	Val	His	Thr	Arg	Phe	Pro	Pro	Glu	Pro	Asn	Gly	Tyr	Leu	His
1				5				10					15		
Ile Gly His Ala Lys Ser Ile Cys Leu Asn Phe Gly Ile Ala															
20 25 30															

(2) INFORMATION FOR SEQ ID NO: 157:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

Lys	Ile	Lys	Leu	Tyr	Cys	Gly	Val	Asp	Pro	Thr	Ala	Gln	Ser	Leu	His
1				5				10					15		
Leu Gly Asn Leu Val Pro Met Val Leu Leu His Phe Tyr Val															
20 25 30															

(2) INFORMATION FOR SEQ ID NO: 158:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:

- 179 -

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

Pro	Ile	Ala	Leu	Tyr	Cys	Gly	Phe	Asp	Pro	Thr	Ala	Asp	Ser	Leu	His
1				5					10					15	
Leu	Gly	His	Leu	Val	Pro	Leu	Leu	Cys	Leu	Lys	Arg	Gly	Gln		
			20					25				30			

(2) INFORMATION FOR SEQ ID NO: 159:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

Arg	Val	Thr	Leu	Tyr	Cys	Gly	Phe	Asp	Pro	Thr	Ala	Asp	Ser	Leu	His
1				5					10					15	
Ile	Gly	Asn	Leu	Ala	Ala	Ile	Leu	Thr	Leu	Arg	Arg	Phe	Gln		
			20					25				30			

(2) INFORMATION FOR SEQ ID NO: 160:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

Arg	Ile	Gly	Ala	Tyr	Val	Gly	Ile	Asp	Pro	Thr	Ala	Pro	Ser	Leu	His
1				5					10					15	
Val	Gly	His	Leu	Leu	Pro	Leu	Met	Pro	Leu	Phe	Trp	Met	Tyr		
			20				25				30				

(2) INFORMATION FOR SEQ ID NO: 161:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

- 180 -

Pro Ile Ala Leu Tyr Cys Gly Phe Asp Pro Thr Ala Asp Ser Leu His  
1 5 10 15

Leu Gly His Leu Val Pro Leu Leu Cys Leu Lys Arg Phe Gln  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 162:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 30 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

Pro Leu Lys Val Lys Leu Gly Ala Asp Pro Thr Ala Pro Asp Ile His  
1 5 10 15

Leu Gly His Thr Val Val Leu Asn Lys Leu Arg Gln Phe Gln  
20 25 30

(2) INFORMATION FOR SEQ ID NO: 163:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 43 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

Val Ser Lys Gly Leu Leu Ile Phe Asp Ala Ser Ser Ser Met Gly Pro  
1 5 10 15

Gln Met Ser Ala Ser Val His Leu Asp Ser Lys Lys Lys Gln His Leu  
20 25 30

Phe Val Lys Glu Val Lys Ile Asp Gly Gln Phe  
35 40

(2) INFORMATION FOR SEQ ID NO: 164:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 43 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe Ser Leu Trp Glu Lys  
1 5 10 15

- 181 -

Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser Phe Asp Leu  
20 25 30

Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His  
35 40

(2) INFORMATION FOR SEQ ID NO: 165:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 39 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

Lys Asn Arg Asn Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu  
1 5 10 15

Thr Lys Ile Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser Gln Asp Glu  
20 25 30

Leu Pro Arg Thr Phe Gln Ile  
35

(2) INFORMATION FOR SEQ ID NO: 166:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 36 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys  
1 5 10 15

Arg Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val  
20 25 30

Glu Gly Ser His  
35

(2) INFORMATION FOR SEQ ID NO: 167:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 42 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

- 182 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

Arg Ala Phe Gly Trp Glu Ala Pro Arg Glu Tyr His Met Pro Leu Leu  
1 5 10 15

Arg Asn Pro Asp Lys Thr Lys Ile Ser Lys Arg Lys Ser His Thr Ser  
20 25 30

Leu Asp Trp Tyr Lys Ala Glu Gly Phe Leu  
35 40

(2) INFORMATION FOR SEQ ID NO: 168:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 42 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

Asp Asn Ile Thr Ile Pro Val His Pro Arg Gln Tyr Glu Phe Ser Arg  
1 5 10 15

Leu Asn Leu Glu Tyr Thr Val Met Ser Lys Arg Lys Leu Asn Leu Leu  
20 25 30

Val Thr Asp Lys His Val Glu Gly Trp Asp  
35 40

(2) INFORMATION FOR SEQ ID NO: 169:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 40 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

Lys Asn Lys Gly Leu Pro Phe Gly Ile Thr Val Pro Leu Leu Thr Thr  
1 5 10 15

Ala Thr Gly Glu Lys Phe Gly Lys Ser Ala Gly Asn Ala Val Phe Ile  
20 25 30

Asp Pro Ser Ile Asn Thr Ala Tyr  
35 40

(2) INFORMATION FOR SEQ ID NO: 170:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 41 amino acids

- 183 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

Arg	Leu	His	Gln	Asn	Gln	Val	Phe	Gly	Leu	Thr	Val	Pro	Leu	Ile	Thr
1						5			10					15	
Lys	Ala	Asp	Gly	Thr	Lys	Phe	Gly	Lys	Thr	Glu	Gly	Gly	Ala	Val	Trp
					20			25					30		
Leu	Asp	Pro	Lys	Lys	Thr	Ser	Pro	Tyr							
			35			40									

(2) INFORMATION FOR SEQ ID NO: 171:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 42 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

Lys	Thr	Lys	Gly	Glu	Ala	Arg	Ala	Phe	Gly	Leu	Thr	Ile	Pro	Leu	Val
1					5					10				15	
Thr	Lys	Ala	Asp	Gly	Thr	Lys	Phe	Gly	Lys	Thr	Glu	Ser	Gly	Thr	Ile
					20				25				30		
Trp	Leu	Asp	Lys	Glu	Lys	Thr	Ser	Pro	Tyr						
			35			40									

(2) INFORMATION FOR SEQ ID NO: 172:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 41 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

Lys	Thr	Ala	Leu	Asp	Glu	Cys	Val	Gly	Phe	Thr	Val	Pro	Leu	Leu	Thr
1							5			10				15	
Asp	Ser	Ser	Gly	Ala	Lys	Phe	Gly	Lys	Ser	Ala	Gly	Asn	Ala	Ile	Trp
					20			25					30		
Leu	Asp	Pro	Tyr	Gln	Thr	Ser	Val	Phe							
			35			40									

- 184 -

(2) INFORMATION FOR SEQ ID NO: 173:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:

Arg Leu His Gln Asn Gln Val Phe Gly Leu Thr Val Pro Leu Ile Thr  
1 5 10 15

Lys Ala Asp Gly Thr Lys Phe Gly Lys Thr Glu Gly Gly Ala Val Trp  
20 25 30

Leu Asp Pro Lys Lys Thr Ser Pro Tyr  
35 40

(2) INFORMATION FOR SEQ ID NO: 174:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

Ser Ala Gly Lys Lys Pro Gln Val Ala Ile Thr Leu Pro Leu Leu Val  
1 5 10 15

Gly Leu Asp Gly Glu Lys Lys Met Ser Lys Ser Leu Gly Asn Tyr Ile  
20 25 30

Gly Val Thr Glu Ala Pro Ser Asp Met Phe  
35 40

(2) INFORMATION FOR SEQ ID NO: 175:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser  
1 5 10 15

Phe Ser Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly  
20 25 30

- 185 -

Leu Lys Leu  
35

(2) INFORMATION FOR SEQ ID NO: 176:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

Lys Leu Gly Gln Gly Cys Phe Gly Glu Val Trp Met Gly Thr Trp Asn  
1 5 10 15

Gly Thr Thr Arg Val Ala Ile Lys Thr Leu Lys Pro Gly  
20 25

(2) INFORMATION FOR SEQ ID NO: 177:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 4 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

His Ile Gly His  
1

(2) INFORMATION FOR SEQ ID NO: 178:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 17 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

His Lys Asn Thr Ser Thr Leu Ser Cys Asp Gly Ser Leu Arg His Lys  
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO: 179:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 17 amino acids

**SUBSTITUTE SHEET (RULE 26)**

- 186 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

Arg Lys Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg  
1                   5                   10                   15

Ala

(2) INFORMATION FOR SEQ ID NO: 180:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys  
1                   5                   10                   15

Gln His

(2) INFORMATION FOR SEQ ID NO: 181:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

Lys Lys Gly Phe Tyr Lys Lys Gln Cys Arg Pro Ser Lys Gly Arg  
1                   5                   10                   15

Lys

(2) INFORMATION FOR SEQ ID NO: 182:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

**SUBSTITUTE SHEET (RULE 26)**

- 187 -

Lys Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg  
1 5 10 15

Glu Arg

(2) INFORMATION FOR SEQ ID NO: 183:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 17 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro Gln Pro Lys Lys  
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 184:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 17 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

Lys Lys Thr Asn Leu Phe Ser Ala Leu Ile Lys Lys Lys Lys Lys Thr  
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 185:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 17 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

Arg Lys Thr Leu Leu Asn Ser Leu Glu Glu Ala Lys Lys Lys Lys Glu  
1 5 10 15

Asp

- 188 -

(2) INFORMATION FOR SEQ ID NO: 186:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 186:

Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg Leu Thr Arg  
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 187:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187:

Arg Arg Ser Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg  
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 188:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 188:

Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys Val Ser Arg Lys His  
1 5 10 15

Phe

- 189 -

(2) INFORMATION FOR SEQ ID NO: 189:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

Lys Arg Val Ala Lys Arg Lys Leu Ile Glu Gln Asn Arg Glu Arg Arg  
1 5 10 15  
**Arg**

(2) INFORMATION FOR SEQ ID NO: 190:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

His Arg Ser Thr Asn Ala Gln Gly Ser His Trp Lys Gln Arg Arg Lys  
1 5 10 15  
**Phe**

(2) INFORMATION FOR SEQ ID NO: 191:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

Lys Arg Pro Pro Ile Ser Asp Ser Glu Glu Leu Ser Ala Lys Lys Arg  
1 5 10 15  
**Lys**

(2) INFORMATION FOR SEQ ID NO: 192:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid

- 190 -

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

Lys Lys Gly Lys Lys Pro Lys Thr Glu Lys Glu Asp Lys Val Lys His  
1 5 10 15

Ile

(2) INFORMATION FOR SEQ ID NO: 193:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 17 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

Arg Lys Arg Met Arg Asn Arg Ile Ala Ala Ser Lys Cys Arg Lys Arg  
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 194:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 194:

Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys  
1 5 10 15

Gln His

(2) INFORMATION FOR SEQ ID NO: 195:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 21 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195:

- 191 -

Lys Lys Ile Thr Glu Val Ala Leu Met Gly His Leu Ser Cys Asp Thr  
1 5 10 15

Lys Glu Glu Arg Lys  
20

(2) INFORMATION FOR SEQ ID NO: 196:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 14 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 196:

Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 197:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 21 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly  
1 5 10 15

Lys Gly Lys Glu Lys  
20

(2) INFORMATION FOR SEQ ID NO: 198:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 18 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu Leu Lys Lys  
1 5 10 15

Thr Lys

- 192 -

(2) INFORMATION FOR SEQ ID NO: 199:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu  
1                   5                   10                   15  
  
Asp Met

(2) INFORMATION FOR SEQ ID NO: 200:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 200:

Lys Ala Gly Lys Leu Lys Phe Ile Ile Pro Ser Pro Lys Arg Pro Val  
1                   5                   10                   15  
  
Lys Leu

(2) INFORMATION FOR SEQ ID NO: 201:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr Lys Lys  
1                   5                   10                   15  
  
Tyr Arg

(2) INFORMATION FOR SEQ ID NO: 202:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids

- 193 -

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:

Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys  
1                       5   10   15  
  
Arg His

(2) INFORMATION FOR SEQ ID NO: 203:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 20 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 203:

Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg  
1                       5   10   15  
  
His Asp Ala His  
20

(2) INFORMATION FOR SEQ ID NO: 204:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 18 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys  
1                       5   10   15  
  
His Arg

(2) INFORMATION FOR SEQ ID NO: 205:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

- 194 -

Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu Lys  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 206:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 15 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:

Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 207:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 14 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 207:

Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg  
1 5 10

(2) INFORMATION FOR SEQ ID NO: 208:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 16 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:

Lys Ser Pro Ala Thr Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys  
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 209:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 20 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 209:

- 195 -

Lys	Tyr	His	Trp	Glu	His	Thr	Gly	Leu	Thr	Leu	Arg	Glu	Val	Ser	Ser
1															15

Lys	Leu	Arg	Arg
			20

## (2) INFORMATION FOR SEQ ID NO: 210:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 21 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 210:

Lys	Asp	Asn	Val	Phe	Asp	Gly	Leu	Val	Arg	Val	Thr	Gln	Lys	Phe	His
1															15
Met	Lys	Val	Lys	His											
				20											

## (2) INFORMATION FOR SEQ ID NO: 211:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 180 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:

Ser	Ile	Asn	Leu	Pro	Phe	Phe	Glu	Thr	Leu	Gln	Glu	Tyr	Phe	Glu	Arg
1															15
Asn	Arg	Gln	Thr	Ile	Ile	Val	Val	Leu	Glu	Asn	Val	Gln	Arg	Lys	Leu
					20									30	
Lys	His	Ile	Asn	Ile	Asp	Gln	Phe	Val	Arg	Lys	Tyr	Arg	Ala	Ala	Leu
					35			40						45	
Gly	Lys	Leu	Pro	Gln	Gln	Ala	Asn	Asp	Tyr	Leu	Asn	Ser	Phe	Asn	Trp
					50			55						60	
Glu	Arg	Gln	Val	Ser	His	Ala	Lys	Glu	Lys	Leu	Thr	Ala	Leu	Thr	Lys
					65			70						80	
Lys	Tyr	Arg	Ile	Thr	Glu	Asn	Asp	Ile	Gln	Ile	Ala	Leu	Asp	Asp	Ala
					85			90						95	
Lys	Ile	Asn	Phe	Asn	Glu	Leu	Ser	Gln	Leu	Gln	Thr	Tyr	Met	Ile	
					100			105					110		

- 196 -

Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu Lys  
115 120 125

Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys Ser  
130 135 140

Leu Asp Glu His Tyr His Ile Arg Val Ile Leu Val Lys Thr Ile His  
145 150 155 160

Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe Asn Lys Ser Gly Ser  
165 170 175

Ser Thr Ala Ser  
180

(2) INFORMATION FOR SEQ ID NO: 212:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 94 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:

Pro Gln Gln Val Asn Asp Tyr Leu Ser Thr Phe Ser Trp Glu Arg Gln  
1 5 10 15

Val Leu Ser Ala Lys Lys Lys His Ser Asp Phe Met Glu Asp Tyr Arg  
20 25 30

Ile Thr Glu Asn Asp Val Arg Ile Ala Leu Asp Asn Ala Lys Ile Asn  
35 40 45

Leu Asn Glu Lys Leu Thr Gln Leu Gln Thr Tyr Val Ile Gln Phe Asp  
50 55 60

Gln Tyr Ile Lys Asp Asn Tyr Asp Leu His Asp Phe Lys Thr Ala Ile  
65 70 75 80

Ala Arg Ile Ile Asp Glu Ile Ile Ala Thr Leu Lys Ile Leu  
85 90

(2) INFORMATION FOR SEQ ID NO: 213:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 85 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 213:

- 197 -

Lys	Tyr	Arg	Val	Ala	Leu	Ser	Arg	Leu	Pro	Gln	Gln	Ile	His	Asp	Tyr
1				5				10					15		
Leu	Asn	Ala	Ser	Asp	Trp	Glu	Arg	Gln	Val	Ala	Gly	Ala	Lys	Glu	Lys
					20			25					30		
Leu	Thr	Ser	Phe	Met	Glu	Asn	Tyr	Arg	Ile	Thr	Asp	Asn	Asp	Val	Leu
						35		40				45			
Ile	Ala	Leu	Asp	Ser	Ala	Lys	Ile	Asn	Leu	Asn	Glu	Lys	Leu	Ser	Gln
						50		55			60				
Leu	Glu	Thr	Tyr	Ala	Ile	Gln	Phe	Asp	Gln	Tyr	Ile	Arg	Asp	Asn	Tyr
					65		70		75			80			
Asp	Ala	Gln	Asp	Leu											
				85											

(2) INFORMATION FOR SEQ ID NO: 214:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 840 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:

Leu	Asn	Asp	Phe	Gln	Val	Pro	Asp	Leu	His	Ile	Pro	Glu	Phe	Gln	Leu
1					5			10				15			
Pro	His	Ile	Ser	His	Thr	Ile	Glu	Val	Pro	Thr	Phe	Gly	Lys	Leu	Tyr
					20			25				30			
Ser	Ile	Leu	Lys	Ile	Gln	Ser	Pro	Leu	Phe	Thr	Leu	Asp	Ala	Asn	Ala
					35			40			45				
Asp	Ile	Gly	Asn	Gly	Thr	Thr	Ser	Ala	Asn	Glu	Ala	Gly	Ile	Ala	Ala
					50			55			60				
Ser	Ile	Thr	Ala	Lys	Gly	Glu	Ser	Lys	Leu	Glu	Val	Leu	Asn	Phe	Asp
					65			70		75			80		
Phe	Gln	Ala	Asn	Ala	Gln	Leu	Ser	Asn	Pro	Lys	Ile	Asn	Pro	Leu	Ala
						85			90			95			
Leu	Lys	Glu	Ser	Val	Lys	Phe	Ser	Ser	Lys	Tyr	Leu	Arg	Thr	Glu	His
						100			105			110			
Gly	Ser	Glu	Met	Leu	Phe	Phe	Gly	Asn	Ala	Ile	Glu	Gly	Lys	Ser	Asn
						115			120			125			
Thr	Val	Ala	Ser	Leu	His	Thr	Glu	Lys	Asn	Thr	Leu	Glu	Leu	Ser	Asn
					130			135			140				

- 198 -

Gly Val Ile Val Lys Ile Asn Asn Gln Leu Thr Leu Asp Ser Asn Thr  
145 150 155 160

Lys Tyr Phe His Lys Leu Asn Ile Pro Lys Leu Asp Phe Ser Ser Gln  
165 170 175

Ala Asp Leu Arg Asn Glu Ile Lys Thr Leu Leu Lys Ala Gly His Ile  
180 185 190

Ala Trp Thr Ser Ser Gly Lys Gly Ser Trp Lys Trp Ala Cys Pro Arg  
195 200 205

Phe Ser Asp Glu Gly Thr His Glu Ser Gln Ile Ser Phe Thr Ile Glu  
210 215 220

Gly Pro Leu Thr Ser Phe Gly Leu Ser Asn Lys Ile Asn Ser Lys His  
225 230 235 240

Leu Arg Val Asn Gln Asn Leu Val Tyr Glu Ser Gly Ser Leu Asn Phe  
245 250 255

Ser Lys Leu Glu Ile Gln Ser Gln Val Asp Ser Gln His Val Gly His  
260 265 270

Ser Val Leu Thr Ala Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala  
275 280 285

Glu Phe Thr Gly Arg His Asp Ala His Leu Asn Gly Lys Val Ile Gly  
290 295 300

Thr Leu Lys Asn Ser Leu Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr  
305 310 315 320

Ala Ser Thr Asn Asn Glu Gly Asn Leu Lys Val Arg Phe Pro Leu Arg  
325 330 335

Leu Thr Gly Lys Ile Asp Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser  
340 345 350

Pro Ser Ala Gln Gln Ala Ser Trp Gln Val Ser Ala Arg Phe Asn Gln  
355 360 365

Tyr Lys Tyr Asn Gln Asn Phe Ser Ala Gly Asn Asn Glu Asn Ile Met  
370 375 380

Glu Ala His Val Gly Ile Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn  
385 390 395 400

Ile Pro Leu Thr Ile Pro Glu Met Arg Leu Pro Tyr Thr Ile Ile Thr  
405 410 415

Thr Pro Pro Leu Lys Asp Phe Ser Leu Trp Glu Lys Thr Gly Leu Lys  
420 425 430

Glu Phe Leu Lys Thr Thr Lys Gln Ser Phe Asp Leu Ser Val Lys Ala  
435 440 445

- 199 -

Gln	Tyr	Lys	Lys	Asn	Lys	His	Arg	His	Ser	Ile	Thr	Asn	Pro	Leu	Ala
450						455							460		
Val	Leu	Cys	Glu	Phe	Ile	Ser	Gln	Ser	Ile	Lys	Ser	Phe	Asp	Arg	His
465					470				475					480	
Phe	Glu	Lys	Asn	Arg	Asn	Asn	Ala	Leu	Asp	Phe	Val	Thr	Lys	Ser	Tyr
					485				490					495	
Asn	Glu	Thr	Lys	Ile	Lys	Phe	Asp	Lys	Tyr	Lys	Ala	Glu	Lys	Ser	Gln
					500			505					510		
Asp	Glu	Leu	Pro	Arg	Thr	Phe	Gln	Ile	Pro	Gly	Tyr	Thr	Val	Pro	Val
					515			520					525		
Val	Asn	Val	Glu	Val	Ser	Pro	Phe	Thr	Ile	Glu	Met	Ser	Ala	Phe	Gly
					530			535			540				
Tyr	Val	Phe	Pro	Lys	Ala	Val	Ser	Met	Pro	Ser	Phe	Ser	Ile	Leu	Gly
					545			550			555			560	
Ser	Asp	Val	Arg	Val	Pro	Ser	Tyr	Thr	Leu	Ile	Leu	Pro	Ser	Leu	Glu
					565			570					575		
Leu	Pro	Val	Leu	His	Val	Pro	Arg	Asn	Leu	Lys	Leu	Ser	Leu	Pro	His
					580			585					590		
Phe	Lys	Glu	Leu	Cys	Thr	Ile	Ser	His	Ile	Phe	Ile	Pro	Ala	Met	Gly
					595			600					605		
Asn	Ile	Thr	Tyr	Asp	Phe	Ser	Phe	Lys	Ser	Ser	Val	Ile	Thr	Leu	Asn
					610			615			620				
Thr	Asn	Ala	Glu	Leu	Phe	Asn	Gln	Ser	Asp	Ile	Val	Ala	His	Leu	Leu
					625			630			635			640	
Ser	Ser	Ser	Ser	Val	Ile	Asp	Ala	Leu	Gln	Tyr	Lys	Leu	Glu	Gly	
					645			650					655		
Thr	Thr	Arg	Leu	Thr	Arg	Lys	Arg	Gly	Leu	Lys	Leu	Ala	Thr	Ala	Leu
					660			665					670		
Ser	Leu	Ser	Asn	Lys	Phe	Val	Glu	Gly	Ser	His	Asn	Ser	Thr	Val	Ser
					675			680					685		
Leu	Thr	Thr	Lys	Asn	Met	Glu	Val	Ser	Val	Ala	Lys	Thr	Thr	Lys	Ala
					690			695			700				
Glu	Ile	Pro	Ile	Leu	Arg	Met	Asn	Phe	Lys	Gln	Glu	Leu	Asn	Gly	Asn
					705			710			715			720	
Thr	Lys	Ser	Lys	Pro	Thr	Val	Ser	Ser	Ser	Met	Glu	Phe	Lys	Tyr	Asp
					725			730					735		

- 200 -

Phe Asn Ser Ser Met Leu Tyr Ser Thr Ala Lys Gly Ala Val Asp His			
740	745	750	
Lys Leu Ser Leu Glu Ser Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser			
755	760	765	
Thr Lys Gly Asp Val Lys Gly Ser Val Leu Ser Arg Glu Tyr Ser Gly			
770	775	780	
Thr Ile Ala Ser Glu Ala Asn Thr Tyr Leu Asn Ser Lys Ser Thr Arg			
785	790	795	800
Ser Ser Val Lys Leu Gln Gly Thr Ser Lys Ile Asp Asp Ile Trp Asn			
805	810	815	
Leu Glu Val Lys Glu Asn Phe Ala Gly Glu Ala Thr Leu Gln Arg Ile			
820	825	830	
Tyr Ser Leu Trp Glu His Ser Thr			
835	840		

## (2) INFORMATION FOR SEQ ID NO: 215:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 774 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

Glu Phe Gln Leu Pro Arg Leu Ser His Thr Ile Glu Ile Pro Ala Phe			
1	5	10	15
Gly Arg Leu His Gly Ile Leu Lys Ile Gln Ser Pro Leu Phe Ile Leu			
20	25	30	
Asp Ala Asn Ala Asn Ile Gln Asn Val Thr Thr Leu Glu Asn Lys Ala			
35	40	45	
Glu Ile Val Ala Ser Ile Ala Ala Thr Gly Glu Ser Glu Ile Glu Ala			
50	55	60	
Leu Asn Phe Asp Phe Gln Ala Gln Phe Leu Glu Leu Asn Pro			
65	70	75	80
Asn Pro Leu Ile Leu Lys Glu Ser Met Asn Phe Ser Ser Lys His Ala			
85	90	95	
Arg Met Glu His Glu Gly Glu Ile Leu Phe Ser Gly Lys Phe Ile Glu			
100	105	110	
Gly Lys Leu Asp Thr Val Ala Ser Leu Gln Thr Glu Lys Asn Met Val			
115	120	125	

- 201 -

Glu Phe Asn Asn Gly Met Ile Val Lys Ile Asn Asn Pro Ile Ile Leu  
130 135 140

Asp Ser His Thr Lys Tyr Phe His Lys Leu Ser Ile Pro Arg Leu Asp  
145 150 155 160

Phe Ser Ser Lys Ala Ser Phe Asn Asn Glu Ile Lys Met Leu Leu Glu  
165 170 175

Ala Gly His Val Ala Trp Thr Ser Ser Gly Thr Gly Ser Trp Asn Trp  
180 185 190

Ala Cys Pro Asn Phe Ser Asp Glu Gly Thr His Ser Ser Lys Ile Ser  
195 200 205

Phe Thr Val Glu Gly Pro Ile Ala Phe Phe Gly Leu Ser Asn Asn Ile  
210 215 220

Asn Gly Lys His Leu Arg Val Ile Gln Lys Leu Ala Tyr Glu Ser Gly  
225 230 235 240

Phe Leu Asn Tyr Ser Met Leu Glu Val Glu Ser Lys Val Glu Ser Gln  
245 250 255

His Val Gly Ser Ser Ile Leu Thr Gly Lys Gly Thr Val Leu Leu Arg  
260 265 270

Glu Ala Lys Ala Glu Met Thr Gly Glu His Asn Ala Asp Leu Asn Gly  
275 280 285

Lys Val Ile Gly Thr Leu Lys Asn Ser Leu Ser Phe Ser Ala Gln Pro  
290 295 300

Phe Met Ile Thr Ala Ser Thr Asn Asn Asp Gly Asn Leu Lys Val Ser  
305 310 315 320

Phe Pro Leu Lys Leu Thr Gly Lys Ile Asp Phe Leu Asn Asn Tyr Ala  
325 330 335

Leu Phe Leu Ser Pro His Ala Gln Gln Ala Ser Trp Gln Val Ser Ala  
340 345 350

Arg Phe Asn Gln Tyr Lys Tyr Asn Gln Asn Phe Ser Ala Ile Asn Asn  
355 360 365

Glu His Asn Ile Glu Ala His Val Gly Met Asn Gly Asp Ala Asn Leu  
370 375 380

Asp Phe Leu Thr Ile Pro Leu Thr Ile Pro Glu Val Lys Leu Pro Tyr  
385 390 395 400

Ile Gly Leu Thr Thr Pro Leu Leu Lys Asp Phe Ser Ile Trp Glu Glu  
405 410 415

Thr Gly Leu Lys Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr  
420 425 430

- 202 -

Lys	Lys	Asn	Arg	Asp	Arg	His	Ser	Ile	Ala	Ile	Pro	Leu	Asn	Gly	Phe
435															445
Tyr	Glu	Phe	Ile	Leu	Asn	Asn	Val	Asp	Ser	Gly	Ile	Gly	Lys	Ile	Gly
450															460
Lys	Val	Arg	Asp	Ser	Ala	Leu	Asp	Tyr	Leu	Ile	Ser	Ser	Tyr	Asn	Glu
465															480
Ala	Lys	Asn	Lys	Phe	Glu	Asn	Ser	Leu	Ile	Gln	Pro	Ser	Arg	Thr	Phe
															485
Gln	Lys	Arg	Gly	Tyr	Thr	Ile	Pro	Phe	Val	Asn	Ile	Glu	Val	Thr	Pro
															505
Phe	Thr	Val	Glu	Thr	Leu	Ala	Ser	Ser	His	Val	Ile	Pro	Lys	Ala	Ile
															515
Asn	Thr	Pro	Ser	Val	His	Ile	Leu	Gly	Pro	Asn	Val	Ile	Val	Pro	Ser
															530
Tyr	Arg	Leu	Val	Leu	Pro	Ser	Leu	Glu	Leu	Pro	Val	Leu	Arg	Val	Pro
															545
Arg	Asn	Leu	Leu	Lys	Phe	Ser	Leu	Pro	Asp	Phe	Lys	Glu	Leu	Arg	Thr
															565
Ile	Asp	Asn	Ile	Tyr	Ile	Pro	Ala	Leu	Gly	Asn	Phe	Thr	Tyr	Asp	Phe
															580
Ser	Phe	Lys	Ser	Ser	Val	Ile	Thr	Leu	Asn	Thr	Asn	Val	Gly	Leu	Tyr
															595
Asn	Arg	Ser	Asp	Ile	Val	Ala	His	Phe	Leu	Ser	Ser	Ser	Ser	Phe	Val
															610
Thr	Asp	Ala	Leu	Gln	Tyr	Lys	Leu	Glu	Gly	Thr	Ser	Arg	Leu	Thr	Arg
															625
Lys	Arg	Gly	Leu	Lys	Leu	Ala	Thr	Ala	Asp	Ser	Leu	Thr	Asn	Lys	Phe
															645
Val	Lys	Gly	Asn	His	Asp	Ser	Thr	Phe	Ser	Leu	Thr	Lys	Lys	Asn	Met
															660
Glu	Ala	Ser	Val	Lys	Thr	Thr	Ala	Asn	Leu	His	Ala	Pro	Ile	Leu	Thr
															675
Met	Asn	Phe	Lys	Gln	Glu	Leu	Asn	Gly	Asn	Ala	Lys	Ser	Lys	Pro	Ile
															690
Val	Ser	Ser	Ser	Ile	Glu	Leu	Asn	Tyr	Asp	Phe	Asn	Ser	Ser	Lys	Leu
															705
															710
															715
															720

- 203 -

Tyr Ser Thr Ala Lys Gly Gly Val Asp His Lys Phe Ser Leu Glu Ser		
725	730	735
Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asn Ile Lys		
740	745	750
Gly Ser Val Leu Ser Gln Glu Tyr Ser Gly Ser Val Ala Ser Glu Ala		
755	760	765
Asn Thr Tyr Leu Asn Ser		
770		

(2) INFORMATION FOR SEQ ID NO: 216:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 785 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:

Glu Phe Gln Leu Pro His Leu Ser His Thr Ile Glu Ile Pro Ala Phe			
1	5	10	15
Gly Lys Leu His Ser Ile Leu Lys Ile Gln Ser Pro Leu Phe Ile Leu			
20	25	30	
Asp Ala Asn Ala Asn Ile Gln Asn Val Thr Thr Ser Gly Asn Lys Ala			
35	40	45	
Glu Ile Val Ala Ser Val Thr Ala Lys Gly Glu Ser Gln Phe Glu Ala			
50	55	60	
Leu Asn Phe Asp Phe Gln Ala Gln Phe Leu Glu Leu Asn Pro			
65	70	75	80
His Pro Pro Val Leu Lys Glu Ser Met Asn Phe Ser Ser Lys His Val			
85	90	95	
Arg Met Glu His Glu Gly Glu Ile Val Phe Asp Gly Lys Ala Ile Glu			
100	105	110	
Gly Lys Ser Asp Thr Val Ala Ser Leu His Thr Glu Lys Asn Glu Val			
115	120	125	
Glu Phe Asn Asn Gly Met Thr Val Lys Val Asn Asn Gln Leu Thr Leu			
130	135	140	
Asp Ser His Thr Lys Tyr Phe His Lys Leu Ser Val Pro Arg Leu Asp			
145	150	155	160
Phe Ser Ser Lys Ala Ser Leu Asn Asn Glu Ile Lys Thr Leu Leu Glu			
165	170	175	

- 204 -

Ala	Gly	His	Val	Ala	Leu	Thr	Ser	Ser	Gly	Thr	Gly	Ser	Trp	Asn	Trp
				180				185						190	
Ala	Cys	Pro	Asn	Phe	Ser	Asp	Glu	Gly	Ile	His	Ser	Ser	Gln	Ile	Ser
				195				200					205		
Phe	Thr	Val	Asp	Gly	Pro	Ile	Ala	Phe	Val	Gly	Leu	Ser	Asn	Asn	Ile
				210				215					220		
Asn	Gly	Lys	His	Leu	Arg	Val	Ile	Gln	Lys	Leu	Thr	Tyr	Glu	Ser	Gly
				225				230			235		240		
Phe	Leu	Asn	Tyr	Ser	Lys	Phe	Glu	Val	Glu	Ser	Lys	Val	Glu	Ser	Gln
				245				250			255				
His	Val	Gly	Ser	Ser	Ile	Leu	Thr	Ala	Asn	Gly	Arg	Ala	Leu	Leu	Lys
				260				265			270				
Asp	Ala	Lys	Ala	Glu	Met	Thr	Gly	Glu	His	Asn	Ala	Asn	Leu	Asn	Gly
				275				280			285				
Lys	Val	Ile	Gly	Thr	Leu	Lys	Asn	Ser	Leu	Phe	Phe	Ser	Ala	Gln	Pro
				290			295			300					
Phe	Glu	Ile	Thr	Ala	Ser	Thr	Asn	Asn	Glu	Gly	Asn	Leu	Lys	Val	Gly
				305			310			315			320		
Phe	Pro	Leu	Lys	Leu	Thr	Gly	Lys	Ile	Asp	Phe	Leu	Asn	Asn	Tyr	Ala
				325			330			335					
Leu	Phe	Leu	Ser	Pro	Arg	Ala	Gln	Gln	Ala	Ser	Trp	Gln	Ala	Ser	Thr
				340			345			350					
Arg	Phe	Asn	Gln	Tyr	Lys	Tyr	Asn	Gln	Asn	Phe	Ser	Ala	Ile	Asn	Asn
				355			360			365					
Glu	His	Asn	Ile	Glu	Ala	Ser	Ile	Gly	Met	Asn	Gly	Asp	Ala	Asn	Leu
				370			375			380					
Asp	Phe	Leu	Asn	Ile	Pro	Leu	Thr	Ile	Pro	Glu	Ile	Asn	Leu	Pro	Tyr
				385			390			395			400		
Thr	Glu	Phe	Lys	Thr	Pro	Leu	Leu	Lys	Asp	Phe	Ser	Ile	Trp	Glu	Glu
				405			410			415					
Thr	Gly	Leu	Lys	Glu	Phe	Leu	Lys	Thr	Thr	Lys	Gln	Ser	Phe	Asp	Leu
				420			425			430					
Ser	Val	Lys	Ala	Gln	Tyr	Lys	Lys	Asn	Ser	Asp	Lys	His	Ser	Ile	Val
				435			440			445					
Val	Pro	Leu	Gly	Met	Phe	Tyr	Glu	Phe	Ile	Leu	Asn	Asn	Val	Asn	Ser
				450			455			460					
Trp	Asp	Arg	Lys	Phe	Glu	Lys	Val	Arg	Asn	Asn	Ala	Leu	His	Phe	Leu
				465			470			475			480		

- 205 -

Thr Thr Ser Tyr Asn Glu Ala Lys Ile Lys Val Asp Lys Tyr Lys Thr  
485 490 495

Glu Asn Ser Leu Asn Gln Pro Ser Gly Thr Phe Gln Asn His Gly Tyr  
500 505 510

Thr Ile Pro Val Val Asn Ile Glu Val Ser Pro Phe Ala Val Glu Thr  
515 520 525

Leu Ala Ser Arg His Val Ile Pro Thr Ala Ile Ser Thr Pro Ser Val  
530 535 540

Thr Ile Pro Gly Pro Asn Ile Met Val Pro Ser Tyr Lys Leu Val Leu  
545 550 555 560

Pro Pro Leu Glu Leu Pro Val Phe His Gly Pro Gly Asn Leu Phe Lys  
565 570 575

Phe Phe Leu Pro Asp Phe Lys Gly Phe Asn Thr Ile Asp Asn Ile Tyr  
580 585 590

Ile Pro Ala Met Gly Asn Phe Thr Tyr Asp Phe Ser Phe Lys Ser Ser  
595 600 605

Val Ile Thr Leu Asn Thr Asn Ala Gly Leu Tyr Asn Gln Ser Asp Ile  
610 615 620

Val Ala His Phe Leu Ser Ser Ser Ser Phe Val Thr Asp Ala Leu Gln  
625 630 635 640

Tyr Lys Leu Glu Gly Thr Ser Arg Leu Met Arg Lys Arg Gly Leu Lys  
645 650 655

Leu Ala Thr Ala Val Ser Leu Thr Asn Lys Phe Val Lys Gly Ser His  
660 665 670

Asp Ser Thr Ile Ser Leu Thr Lys Lys Asn Met Glu Ala Ser Val Arg  
675 680 685

Thr Thr Ala Asn Leu His Ala Pro Ile Phe Ser Met Asn Phe Lys Gln  
690 695 700

Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val Ser Ser Ser Ile  
705 710 715 720

Glu Leu Asn Tyr Asp Phe Asn Ser Ser Lys Leu His Ser Thr Ala Thr  
725 730 735

Gly Gly Ile Asp His Lys Phe Ser Leu Glu Ser Leu Thr Ser Tyr Phe  
740 745 750

Ser Ile Glu Ser Phe Thr Lys Gly Asn Ile Lys Ser Ser Phe Leu Ser  
755 760 765

- 206 -

Gln Glu Tyr Ser Gly Ser Val Ala Asn Glu Ala Asn Val Tyr Leu Asn  
 770                    775                    780

Ser  
 785

(2) INFORMATION FOR SEQ ID NO: 217:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1056 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:

Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn Thr Tyr Leu Asn Ser  
 1                    5                    10                    15

Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly Thr Ser Lys Ile Asp  
 20                    25                    30

Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe Ala Gly Glu Ala Thr  
 35                    40                    45

Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser Thr Lys Asn His Leu  
 50                    55                    60

Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu His Thr Ser Lys Ala  
 65                    70                    75                    80

Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu Val Gln Val His  
 85                    90                    95

Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp Leu Gly Gln Glu  
 100                    105                    110

Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile Arg Trp Lys Asn  
 115                    120                    125

Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln Val Glu Leu Ser  
 130                    135                    140

Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly Ser Leu Glu Gly  
 145                    150                    155                    160

His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro Val Tyr Asp Lys Ser  
 165                    170                    175

Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg  
 180                    185                    190

Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn  
 195                    200                    205

- 207 -

Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile  
210 215 220

Thr Pro Gly Leu Lys Leu Asn Asp Leu Asn Ser Val Leu Val Met Pro  
225 230 235 240

Thr Phe His Val Pro Phe Thr Asp Leu Gln Val Pro Ser Cys Lys Leu  
245 250 255

Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg Thr Ser Ser Phe  
260 265 270

Ala Leu Asn Leu Pro Thr Leu Pro Glu Val Lys Phe Pro Glu Val Asp  
275 280 285

Val Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile Pro Phe Phe  
290 295 300

Glu Ile Thr Val Pro Glu Ser Gln Leu Thr Val Ser Arg Phe Thr Leu  
305 310 315 320

Pro Lys Ser Val Ser Asp Gly Ile Ala Ala Leu Asp Leu Asn Ala Val  
325 330 335

Ala Asn Lys Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile Val Pro Glu  
340 345 350

Gln Thr Ile Glu Ile Pro Ser Ile Lys Phe Ser Val Pro Ala Gly Ile  
355 360 365

Val Ile Pro Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu Val Asp Ser  
370 375 380

Pro Val Tyr Asn Ala Thr Trp Ser Ala Ser Leu Lys Asn Lys Ala Asp  
385 390 395 400

Tyr Val Glu Thr Val Leu Asp Ser Thr Cys Ser Ser Thr Val Gln Phe  
405 410 415

Leu Glu Tyr Glu Leu Asn Val Leu Gly Thr His Lys Ile Glu Asp Gly  
420 425 430

Thr Leu Ala Ser Lys Thr Lys Gly Thr Leu Ala His Arg Asp Phe Ser  
435 440 445

Ala Glu Tyr Glu Glu Asp Gly Lys Phe Glu Gly Leu Gln Glu Trp Glu  
450 455 460

Gly Lys Ala His Leu Asn Ile Lys Ser Pro Ala Phe Thr Asp Leu His  
465 470 475 480

Leu Arg Tyr Gln Lys Asp Lys Lys Gly Ile Ser Thr Ser Ala Ala Ser  
485 490 495

Pro Ala Val Gly Thr Val Gly Met Asp Met Asp Glu Asp Asp Asp Phe  
500 505 510

- 208 -

Ser Lys Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp Lys Lys  
515 520 525

Leu Thr Ile Phe Lys Thr Glu Leu Arg Val Arg Glu Ser Asp Glu Glu  
530 535 540

Thr Gln Ile Lys Val Asn Trp Glu Glu Ala Ala Ser Gly Leu Leu  
545 550 555 560

Thr Ser Leu Lys Asp Asn Val Pro Lys Ala Thr Gly Val Leu Tyr Asp  
565 570 575

Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu Thr Leu Arg Glu  
580 585 590

Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala Glu Trp Val  
595 600 605

Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val Arg Phe Gln  
610 615 620

Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln Glu Trp Lys Asp Lys  
625 630 635 640

Ala Gln Asn Leu Tyr Gln Glu Leu Leu Thr Gln Glu Gly Gln Ala Ser  
645 650 655

Phe Gln Gly Leu Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr  
660 665 670

Gln Lys Phe His Met Lys Val Lys His Leu Ile Asp Ser Leu Ile Asp  
675 680 685

Phe Leu Asn Phe Pro Arg Phe Gln Phe Pro Gly Lys Pro Gly Ile Tyr  
690 695 700

Thr Arg Glu Glu Leu Cys Thr Met Phe Ile Arg Glu Val Gly Thr Val  
705 710 715 720

Leu Ser Gln Val Tyr Ser Lys Val His Asn Gly Ser Glu Ile Leu Phe  
725 730 735

Ser Tyr Phe Gln Asp Leu Val Ile Thr Leu Pro Phe Glu Leu Arg Lys  
740 745 750

His Lys Leu Ile Asp Val Ile Ser Met Tyr Arg Glu Leu Leu Lys Asp  
755 760 765

Leu Ser Lys Glu Ala Gln Glu Val Phe Lys Ala Ile Gln Ser Leu Lys  
770 775 780

Thr Thr Glu Val Leu Arg Asn Leu Gln Asp Leu Leu Gln Phe Ile Phe  
785 790 795 800

- 209 -

Gln	Leu	Ile	Glu	Asp	Asn	Ile	Lys	Gln	Leu	Lys	Glu	Met	Lys	Phe	Thr	
805									810							815
Tyr	Leu	Ile	Asn	Tyr	Ile	Gln	Asp	Glu	Ile	Asn	Thr	Ile	Phe	Asn	Asp	
820									825							830
Tyr	Ile	Pro	Tyr	Val	Phe	Lys	Leu	Leu	Lys	Glu	Asn	Leu	Cys	Leu	Asn	
835									840							845
Leu	His	Lys	Phe	Asn	Glu	Phe	Ile	Gln	Asn	Glu	Leu	Gln	Glu	Ala	Ser	
850									855							860
Gln	Glu	Leu	Gln	Gln	Ile	His	Gln	Tyr	Ile	Met	Ala	Leu	Arg	Glu	Glu	
865									870							880
Tyr	Phe	Asp	Pro	Ser	Ile	Val	Gly	Trp	Thr	Val	Lys	Tyr	Tyr	Glu	Leu	
885									890							895
Glu	Glu	Lys	Ile	Val	Ser	Leu	Ile	Lys	Asn	Leu	Leu	Val	Ala	Leu	Lys	
900									905							910
Asp	Phe	His	Ser	Glu	Tyr	Ile	Val	Ser	Ala	Ser	Asn	Phe	Thr	Ser	Gln	
915									920							925
Leu	Ser	Ser	Gln	Val	Glu	Gln	Phe	Leu	His	Arg	Asn	Ile	Gln	Glu	Tyr	
930									935							940
Leu	Ser	Ile	Leu	Thr	Asp	Pro	Asp	Gly	Lys	Gly	Lys	Glu	Lys	Ile	Ala	
945									950							960
Glu	Leu	Ser	Ala	Thr	Ala	Gln	Glu	Ile	Ile	Lys	Ser	Gln	Ala	Ile	Ala	
965									970							975
Thr	Lys	Ile	Ile	Ser	Asp	Tyr	His	Gln	Gln	Phe	Arg	Tyr	Lys	Leu		
980									985							990
Gln	Asp	Phe	Ser	Asp	Gln	Leu	Ser	Asp	Tyr	Tyr	Glu	Lys	Phe	Ile	Ala	
995									1000							1005
Glu	Ser	Lys	Arg	Leu	Ile	Asp	Leu	Ser	Ile	Gln	Asn	Tyr	His	Thr	Phe	
1010									1015							1020
Leu	Ile	Tyr	Ile	Thr	Glu	Leu	Leu	Lys	Leu	Gln	Ser	Thr	Thr	Val		
1025									1030							1040
Met	Asn	Pro	Tyr	Met	Lys	Leu	Ala	Pro	Gly	Glu	Leu	Thr	Ile	Ile	Leu	
1045									1050							1055

(2) INFORMATION FOR SEQ ID NO: 218:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 989 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

- 210 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:

Asn Ser Lys Gly Thr Arg Ser Ser Val Arg Leu Gln Gly Ala Ser Asn  
1 5 10 15

Phe Ala Gly Ile Trp Asn Phe Glu Val Gly Glu Asn Phe Ala Gly Glu  
20 25 30

Ala Thr Leu Arg Arg Ile Tyr Gly Thr Trp Glu His Asn Met Ile Asn  
35 40 45

His Leu Gln Val Phe Ser Tyr Phe Asp Thr Lys Gly Lys Gln Thr Cys  
50 55 60

Arg Ala Thr Leu Glu Leu Ser Pro Trp Thr Met Ser Thr Leu Leu Gln  
65 70 75 80

Val His Val Ser Gln Pro Ser Pro Leu Phe Asp Leu His His Phe Asp  
85 90 95

Gln Glu Val Ile Leu Lys Ala Ser Thr Lys Asn Gln Lys Val Ser Trp  
100 105 110

Lys Ser Glu Val Gln Val Glu Ser Gln Val Leu Gln His Asn Ala His  
115 120 125

Phe Ser Asn Asp Gln Glu Glu Val Arg Leu Asp Ile Ala Gly Ser Leu  
130 135 140

Glu Gly Gln Leu Trp Asp Leu Glu Asn Phe Phe Leu Pro Ala Phe Gly  
145 150 155 160

Lys Ser Leu Arg Glu Leu Leu Gln Ile Asp Gly Lys Arg Gln Tyr Leu  
165 170 175

Gln Ala Ser Thr Ser Leu His Tyr Thr Lys Asn Pro Asn Gly Tyr Leu  
180 185 190

Leu Ser Leu Pro Val Gln Glu Leu Thr Asp Arg Phe Ile Ile Pro Gly  
195 200 205

Leu Lys Leu Asn Asp Phe Ser Gly Ile Lys Ile Tyr Lys Lys Leu Ser  
210 215 220

Thr Ser Pro Phe Ala Leu Asn Leu Thr Met Leu Pro Lys Val Lys Phe  
225 230 235 240

Pro Gly Val Asp Leu Leu Thr Gln Tyr Ser Lys Pro Glu Gly Ser Ser  
245 250 255

Val Pro Thr Phe Glu Thr Thr Ile Pro Glu Ile Gln Leu Thr Val Ser  
260 265 270

Gln Phe Thr Leu Pro Lys Ser Phe Pro Val Gly Asn Thr Val Phe Asp  
275 280 285

- 211 -

Leu Asn Lys Leu Thr Asn Leu Ile Ala Asp Val Asp Leu Pro Ser Ile  
290 295 300

Thr Leu Pro Glu Gln Thr Ile Glu Ile Pro Ser Leu Glu Phe Ser Val  
305 310 315 320

Pro Ala Gly Ile Phe Ile Pro Phe Gly Glu Leu Thr Ala His Val  
325 330 335

Gly Met Ala Ser Pro Leu Tyr Asn Val Thr Trp Ser Thr Gly Trp Lys  
340 345 350

Asn Lys Ala Asp His Val Glu Thr Phe Leu Asp Ser Thr Cys Ser Ser  
355 360 365

Thr Leu Gln Phe Leu Glu Tyr Ala Leu Lys Val Val Gly Thr His Arg  
370 375 380

Ile Glu Asn Asp Lys Phe Ile Tyr Lys Ile Lys Gly Thr Leu Gln His  
385 390 395 400

Cys Asp Phe Asn Val Lys Tyr Asn Glu Asp Gly Ile Phe Glu Gly Leu  
405 410 415

Trp Asp Leu Glu Gly Glu Ala His Leu Asp Ile Thr Ser Pro Ala Leu  
420 425 430

Thr Asp Phe His Leu His Tyr Lys Glu Asp Lys Thr Ser Val Ser Ala  
435 440 445

Ser Ala Ala Ser Pro Ala Ile Gly Thr Val Ser Leu Asp Ala Ser Thr  
450 455 460

Asp Asp Gln Ser Val Arg Leu His Val Tyr Phe Arg Pro Gln Ser Pro  
465 470 475 480

Pro Asp Asn Lys Leu Ser Ile Phe Lys Met Glu Trp Arg Asp Lys Glu  
485 490 495

Ser Asp Gly Glu Thr Tyr Ile Lys Ile Asn Trp Glu Glu Ala Ala  
500 505 510

Phe Arg Leu Leu Asp Ser Leu Lys Ser Asn Val Pro Lys Ala Ser Glu  
515 520 525

Ala Val Tyr Asp Tyr Val Lys Lys Tyr His Leu Gly His Ala Ser Ser  
530 535 540

Glu Leu Arg Lys Ser Leu Gln Asn Asp Ala Glu His Ala Ile Arg Met  
545 550 555 560

Val Asp Glu Met Asn Val Asn Ala Gln Arg Val Thr Arg Asp Thr Tyr  
565 570 575

- 212 -

Gln Ser Leu Tyr Lys Lys Met Leu Ala Gln Glu Ser Gln Ser Ile Pro  
580 585 590

Glu Lys Leu Lys Lys Met Val Leu Gly Ser Leu Val Arg Ile Thr Gln  
595 600 605

Lys Tyr His Met Ala Val Thr Trp Leu Met Asp Ser Val Ile His Phe  
610 615 620

Leu Lys Phe Asn Arg Val Gln Phe Pro Gly Asn Ala Gly Thr Tyr Thr  
625 630 635 640

Val Asp Glu Leu Tyr Thr Ile Ala Met Arg Glu Thr Lys Lys Leu Leu  
645 650 655

Ser Gln Leu Phe Asn Gly Leu Gly His Leu Phe Ser Tyr Val Gln Asp  
660 665 670

Gln Val Glu Lys Ser Arg Val Ile Asn Asp Ile Thr Phe Lys Cys Pro  
675 680 685

Phe Ser Pro Thr Pro Cys Lys Leu Lys Asp Val Leu Leu Ile Phe Arg  
690 695 700

Glu Asp Leu Asn Ile Leu Ser Asn Leu Gly Gln Gln Asp Ile Asn Phe  
705 710 715 720

Thr Thr Ile Leu Ser Asp Phe Gln Ser Phe Leu Glu Arg Leu Leu Asp  
725 730 735

Ile Ile Glu Glu Lys Ile Glu Cys Leu Lys Asn Asn Glu Ser Thr Cys  
740 745 750

Val Pro Asp His Ile Asn Met Phe Phe Lys Thr His Ile Pro Phe Ala  
755 760 765

Phe Lys Ser Leu Arg Glu Asn Ile Tyr Ser Val Phe Ser Glu Phe Asn  
770 775 780

Asp Phe Val Gln Ser Ile Leu Gln Glu Gly Ser Tyr Lys Leu Gln Gln  
785 790 795 800

Val His Gln Tyr Met Lys Ala Phe Arg Glu Glu Tyr Phe Asp Pro Ser  
805 810 815

Val Val Gly Trp Thr Val Lys Tyr Tyr Glu Ile Glu Glu Lys Met Val  
820 825 830

Asp Leu Ile Lys Thr Leu Leu Ala Pro Leu Arg Asp Phe Tyr Ser Glu  
835 840 845

Tyr Ser Val Thr Ala Ala Asp Phe Ala Ser Lys Met Ser Thr Gln Val  
850 855 860

Glu Gln Phe Val Ser Arg Asp Ile Arg Glu Tyr Leu Ser Met Leu Ala  
865 870 875 880

- 213 -

Asp Ile Asn Gly Lys Gly Arg Glu Lys Val Ala Glu Leu Ser Ile Val		
885	890	895
Val Lys Glu Arg Ile Lys Ser Trp Ser Thr Ala Val Ala Glu Ile Thr		
900	905	910
Ser Asp Tyr Leu Arg Gln Leu His Ser Lys Leu Gln Asp Phe Ser Asp		
915	920	925
Gln Leu Ser Gly Tyr Tyr Glu Lys Phe Val Ala Glu Ser Thr Arg Leu		
930	935	940
Ile Asp Leu Ser Ile Gln Asn Tyr His Met Phe Leu Arg Tyr Ile Ala		
945	950	955
Glu Leu Leu Lys Lys Leu Gln Val Ala Thr Ala Asn Asn Val Ser Pro		
965	970	975
Tyr Leu Arg Phe Ala Gln Gly Glu Leu Ile Ile Thr Phe		
980	985	

(2) INFORMATION FOR SEQ ID NO: 219:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 396 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:

Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His		
1	5	10
15		
Met Lys Val Lys His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe		
20	25	30
Pro Arg Phe Gln Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu		
35	40	45
Leu Cys Thr Met Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val		
50	55	60
Tyr Ser Lys Val His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln		
65	70	75
80		
Asp Leu Val Ile Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile		
85	90	95
Asp Val Ile Ser Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu		
100	105	110
Ala Gln Glu Val Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu Val		
115	120	125

- 214 -

Leu Arg Asn Leu Gln Asp Leu Leu Gln Phe Ile Phe Gln Leu Ile Glu  
130 135 140

Asp Asn Ile Lys Gln Leu Lys Glu Met Lys Phe Thr Tyr Leu Ile Asn  
145 150 155 160

Tyr Ile Gln Asp Glu Ile Asn Thr Ile Phe Asn Asp Tyr Ile Pro Tyr  
165 170 175

Val Phe Lys Leu Leu Lys Glu Asn Leu Cys Leu Asn Leu His Lys Phe  
180 185 190

Asn Glu Phe Ile Gln Asn Glu Leu Gln Glu Ala Ser Gln Glu Leu Gln  
195 200 205

Gln Ile His Gln Tyr Ile Met Ala Leu Arg Glu Glu Tyr Phe Asp Pro  
210 215 220

Ser Ile Val Gly Trp Thr Val Lys Tyr Glu Leu Glu Glu Lys Ile  
225 230 235 240

Val Ser Leu Ile Lys Asn Leu Leu Val Ala Leu Lys Asp Phe His Ser  
245 250 255

Glu Tyr Ile Val Ser Ala Ser Asn Phe Thr Ser Gln Leu Ser Ser Gln  
260 265 270

Val Glu Gln Phe Leu His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu  
275 280 285

Thr Asp Pro Asp Gly Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala  
290 295 300

Thr Ala Gln Glu Ile Ile Lys Ser Gln Ala Ile Ala Thr Lys Lys Ile  
305 310 315 320

Ile Ser Asp Tyr His Gln Gln Phe Arg Tyr Lys Leu Gln Asp Phe Ser  
325 330 335

Asp Gln Leu Ser Asp Tyr Tyr Glu Lys Phe Ile Ala Glu Ser Lys Arg  
340 345 350

Leu Ile Asp Leu Ser Ile Gln Asn Tyr His Thr Phe Leu Ile Tyr Ile  
355 360 365

Thr Glu Leu Leu Lys Lys Leu Gln Ser Thr Thr Val Met Asn Pro Tyr  
370 375 380

Met Lys Leu Ala Pro Gly Glu Leu Thr Ile Ile Leu  
385 390 395

(2) INFORMATION FOR SEQ ID NO: 220:

(i) SEQUENCE CHARACTERISTICS:

**SUBSTITUTE SHEET (RULE 26)**

- 215 -

- (A) LENGTH: 433 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:

Ile Pro Gly Leu Ser Glu Lys Tyr Thr Gly Glu Glu Leu Tyr Leu Met  
1 5 10 15

Thr Thr Glu Lys Ala Ala Lys Thr Ala Asp Ile Cys Leu Ser Lys Leu  
20 25 30

Gln Glu Tyr Phe Asp Ala Leu Ile Ala Ala Ile Ser Glu Leu Glu Val  
35 40 45

Arg Val Pro Ala Ser Glu Thr Ile Leu Arg Gly Arg Asn Val Leu Asp  
50 55 60

Gln Ile Lys Glu Met Leu Lys His Leu Gln Glu Lys Ile Arg Gln Thr  
65 70 75 80

Phe Val Thr Leu Gln Glu Ala Asp Phe Ala Gly Lys Leu Asn Arg Leu  
85 90 95

Lys Gln Val Val Gln Lys Thr Phe Gln Lys Ala Gly Asn Met Val Arg  
100 105 110

Ser Leu Gln Ser Lys Asn Phe Glu Asp Ile Lys Val Gln Met Gln Gln  
115 120 125

Leu Tyr Lys Asp Ala Met Ala Ser Asp Tyr Ala His Lys Leu Arg Ser  
130 135 140

Leu Ala Glu Asn Val Lys Lys Tyr Ile Ser Gln Ile Lys Asn Phe Ser  
145 150 155 160

Gln Lys Thr Leu Gln Lys Leu Ser Glu Asn Leu Gln Gln Leu Val Leu  
165 170 175

Tyr Ile Lys Ala Leu Arg Glu Glu Tyr Phe Asp Pro Thr Thr Leu Gly  
180 185 190

Trp Ser Val Lys Tyr Tyr Glu Val Glu Asp Lys Val Leu Gly Leu Leu  
195 200 205

Lys Asn Leu Met Asp Thr Leu Val Ile Trp Tyr Asn Glu Tyr Ala Lys  
210 215 220

Asp Leu Ser Asp Leu Val Thr Arg Leu Thr Asp Gln Val Arg Glu Leu  
225 230 235 240

Val Glu Asn Tyr Arg Gln Glu Tyr Tyr Asp Leu Ile Thr Asp Val Glu  
245 250 255

- 216 -

Gly Lys Gly Arg Gln Lys Val Met Glu Leu Ser Ser Ala Ala Gln Glu			
260	265	270	
Lys Ile Arg Tyr Trp Ser Ala Val Ala Lys Arg Lys Ile Asn Glu His			
275	280	285	
Asn Arg Gln Val Lys Ala Lys Leu Gln Glu Ile Tyr Gly Gln Leu Ser			
290	295	300	
Asp Ser Gln Glu Lys Leu Ile Asn Val Ala Lys Met Leu Ile Asp Leu			
305	310	315	320
Thr Val Glu Lys Tyr Ser Thr Phe Met Lys Tyr Ile Phe Glu Leu Leu			
325	330	335	
Arg Trp Phe Glu Gln Ala Thr Ala Asp Ser Ile Lys Pro Tyr Ile Ala			
340	345	350	
Val Arg Glu Gly Glu Leu Arg Ile Asp Val Pro Phe Asp Trp Glu Tyr			
355	360	365	
Ile Asn Gln Met Pro Gln Lys Ser Arg Glu Ala Leu Arg Asn Lys Val			
370	375	380	
Glu Leu Thr Arg Ala Leu Ile Gln Gln Gly Val Glu Gln Gly Thr Arg			
385	390	395	400
Lys Trp Glu Glu Met Gln Ala Phe Ile Asp Glu Gln Leu Ala Thr Glu			
405	410	415	
Gln Leu Ser Phe Gln Gln Ile Val Glu Asn Ile Gln Lys Arg Met Lys			
420	425	430	

Thr

(2) INFORMATION FOR SEQ ID NO: 221:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 180 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:

Asp Met Thr Phe Ser Lys Gln Asn Ala Leu Leu Arg Ser Glu Tyr Gln			
1	5	10	15
Ala Asp Tyr Glu Ser Leu Arg Phe Phe Ser Leu Leu Ser Gly Ser Leu			
20	25	30	
Asn Ser His Gly Leu Glu Leu Asn Ala Asp Ile Leu Gly Thr Asp Lys			
35	40	45	

- 217 -

Ile Asn Ser Gly Ala His Lys Ala Thr Leu Arg Ile Gly Gln Asp Gly			
50	55	60	
Ile Ser Thr Ser Ala Thr Thr Asn Leu Lys Cys Ser Leu Leu Val Leu			
65	70	75	80
Glu Asn Glu Leu Asn Ala Glu Leu Gly Leu Ser Gly Ala Ser Met Lys			
85	90	95	
Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn Ala Lys Phe Ser Leu			
100	105	110	
Asp Gly Lys Ala Ala Leu Thr Glu Leu Ser Leu Gly Ser Ala Tyr Gln			
115	120	125	
Ala Met Ile Leu Gly Val Asp Ser Lys Asn Ile Phe Asn Phe Lys Val			
130	135	140	
Ser Gln Glu Gly Leu Lys Leu Ser Asn Asp Met Met Gly Ser Tyr Ala			
145	150	155	160
Glu Met Lys Phe Asp His Thr Asn Ser Leu Asn Ile Ala Gly Leu Ser			
165	170	175	
Leu Asp Phe Ser			
180			

(2) INFORMATION FOR SEQ ID NO: 222:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 142 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:

Asp Leu Thr Phe Ser Lys Gln Asn Ala Leu Leu Arg Ala Glu Tyr Gln			
1	5	10	15
Ala Asp Tyr Lys Ser Leu Arg Phe Phe Thr Leu Leu Ser Gly Leu Leu			
20	25	30	
Asn Thr His Gly Leu Glu Leu Asn Ala Asp Ile Leu Gly Thr Asp Lys			
35	40	45	
Met Asn Thr Ala Ala His Lys Ala Thr Leu Arg Ile Gly Gln Asn Gly			
50	55	60	
Val Ser Thr Ser Ala Thr Thr Ser Leu Arg Tyr Ser Pro Leu Met Leu			
65	70	75	80
Glu Asn Glu Leu Asn Ala Glu Leu Ala Leu Ser Gly Ala Ser Met Lys			
85	90	95	

- 218 -

Leu Ala Thr Asn Gly Arg Phe Lys Glu His Asn Ala Lys Phe Ser Leu		
100	105	110
Asp Gly Lys Ala Thr Leu Thr Glu Leu Ser Leu Gly Ser Ala Tyr Gln		
115	120	125
Ala Met Ile Leu Gly Ala Asp Ser Lys Asn Ile Phe Asn Phe		
130	135	140

(2) INFORMATION FOR SEQ ID NO: 223:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 420 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 223:

His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe Ser Phe		
1	5	10
Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn Gln		
20	25	30
Ser Asp Ile Val Ala His Leu Leu Ser Ser Ser Ser Val Ile Asp		
35	40	45
Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg		
50	55	60
Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu		
65	70	75
Gly Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val		
85	90	95
Ser Val Ala Lys Thr Thr Lys Ala Glu Ile Pro Ile Leu Arg Met Asn		
100	105	110
Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val Ser		
115	120	125
Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr Ser		
130	135	140
Thr Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu Glu Ser Leu Thr		
145	150	155
160		
Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asp Val Lys Gly Ser		
165	170	175
Val Leu Ser Arg Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn Thr		
180	185	190

- 219 -

Tyr Leu Asn Ser Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly Thr  
195 200 205

Ser Lys Ile Asp Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe Ala  
210 215 220

Gly Glu Ala Thr Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser Thr  
225 230 235 240

Lys Asn His Leu Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu His  
245 250 255

Thr Ser Lys Ala Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu  
260 265 270

Val Gln Val His Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp  
275 280 285

Leu Gly Gln Glu Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile  
290 295 300

Arg Trp Lys Asn Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln  
305 310 315 320

Val Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly  
325 330 335

Ser Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro Val  
340 345 350

Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser  
355 360 365

Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr  
370 375 380

Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala  
385 390 395 400

Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn Asp Leu Asn Ser Val  
405 410 415

Leu Val Met Pro  
420

(2) INFORMATION FOR SEQ ID NO: 224:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 275 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:

- 220 -

Met	Ala	Ser	Glu	Lys	Gly	Pro	Ser	Asn	Lys	Asp	Tyr	Thr	Leu	Arg	Arg
1			5					10					15		
Arg	Ile	Glu	Pro	Trp	Glu	Phe	Glu	Val	Phe	Phe	Asp	Pro	Gln	Glu	Leu
		20					25					30			
Arg	Lys	Glu	Ala	Cys	Leu	Leu	Tyr	Glu	Ile	Lys	Trp	Gly	Ala	Ser	Ser
	35						40					45			
Lys	Thr	Trp	Arg	Ser	Ser	Gly	Lys	Asn	Thr	Thr	Asn	His	Val	Glu	Val
	50					55					60				
Asn	Phe	Leu	Glu	Lys	Leu	Thr	Arg	Lys	Glu	Ala	Cys	Leu	Leu	Tyr	Glu
	65				70				75				80		
Ile	Lys	Trp	Gly	Ala	Ser	Ser	Lys	Thr	Trp	Arg	Ser	Ser	Gly	Lys	Asn
		85					90					95			
Thr	Thr	Asn	His	Val	Glu	Val	Asn	Phe	Leu	Glu	Lys	Leu	Thr	Ser	Glu
		100					105					110			
Gly	Arg	Leu	Gly	Pro	Ser	Thr	Cys	Cys	Ser	Ile	Thr	Trp	Phe	Leu	Ser
		115					120					125			
Trp	Ser	Pro	Cys	Trp	Glu	Cys	Ser	Met	Ala	Ile	Arg	Glu	Phe	Leu	Ser
		130				135					140				
Gln	His	Pro	Gly	Val	Thr	Leu	Ile	Ile	Phe	Val	Ala	Arg	Leu	Phe	Gln
	145					150				155			160		
His	Met	Asp	Arg	Arg	Asn	Arg	Gln	Gly	Leu	Lys	Asp	Leu	Val	Thr	Ser
		165				170						175			
Gly	Val	Thr	Val	Arg	Val	Met	Ser	Val	Ser	Glu	Tyr	Cys	Tyr	Cys	Trp
		180					185					190			
Glu	Asn	Phe	Val	Asn	Tyr	Pro	Pro	Gly	Lys	Ala	Ala	Gln	Trp	Pro	Arg
		195					200					205			
Tyr	Pro	Pro	Arg	Trp	Met	Leu	Met	Tyr	Ala	Leu	Glu	Leu	Tyr	Cys	Ile
		210				215					220				
Ile	Leu	Gly	Leu	Pro	Pro	Cys	Leu	Lys	Ile	Ser	Arg	Arg	His	Gln	Lys
	225					230				235			240		
Gln	Leu	Thr	Phe	Phe	Ser	Leu	Thr	Pro	Gln	Tyr	Cys	His	Tyr	Lys	Met
		245					250					255			
Ile	Pro	Pro	Tyr	Ile	Leu	Leu	Ala	Thr	Gly	Leu	Leu	Gln	Pro	Ser	Val
		260					265					270			
Pro	Trp	Arg													
		275													

- 221 -

(2) INFORMATION FOR SEQ ID NO: 225:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 589 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

GGATCTGACG GTTCACTAAA CCAGCTCTGC TTATATAGAC CTCCCACCGT ACACGCCTAC	60
CGCCCATTG CGTCAATGGG GCGGAGTTGT TACGACATTT TGGAAAGTCC CGTTGATTTT	120
GGTGCCAAAA CAAACTCCAT TGACGTCAAT GGGGTGGAGA CTTGGAAATC CCCGTGAGTC	180
AAACCGCTAT CCACGCCCAT TGATGTACTG CCAAAACCGC ATCACCATGG TAATAGCGAT	240
GACTAATACG TAGATGTACT GCCAAGTAGG AAAGTCCCAT AAGGTCATGT ACTGGGCATA	300
ATGCCAGGGCG GGCCATTAC CGTCATTGAC GTCAATAGGG GCGTACTTG GCATATGATA	360
CACTTGATGT ACTGCCAAGT GGGCAGTTA CCGTAAATAC TCCACCCATT GACGTCAATG	420
GAAAGTCCCT ATTGGCGTTA CTATGGGAAC ATACGTCAATT TGACGTCA ATGGGCGGGG	480
GTCGTTGGGC GGTCAGCCAG GCGGGCCATT TACCGTAAGT TATGTAACGC GGAACTCCAT	540
ATATGGGCTA TGAACTAATG ACCCCGTAAT TGATTACTAT TAATAACTA	589

(2) INFORMATION FOR SEQ ID NO: 226:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 35 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

GATCCAAATC ACCCACTGCA ACTCCTCCCC CTGCG	35
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(2) INFORMATION FOR SEQ ID NO: 227:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

GATCCATCCA ATTGGGAAT CAGGAG	26
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- 222 -

(2) INFORMATION FOR SEQ ID NO: 228:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:

GATCCGGTCT CCAATTGG

18

(2) INFORMATION FOR SEQ ID NO: 229:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:

GATCCTCGGG AAAGGGAAAC CGAAACTGAA GCCG

34

**CLAIMS:**

1. A composition comprising:
  - (a) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and
  - (b) a nucleic acid comprising an LDL or VLDL binding sequence, wherein said nucleic acid is bound to said polypeptide.
2. The composition of claim 1, wherein said polypeptide comprises an LDL nucleic acid binding domain.
3. The composition of claim 1, wherein said polypeptide comprises a VLDL nucleic acid binding domain.
4. The composition of claim 1, wherein said nucleic acid comprises an expression region operably linked to a promoter active in eukaryotic cells.
5. The composition of claim 4, wherein said expression region encodes a polypeptide.
6. The composition of claim 4, wherein said expression region comprises an antisense construct.
7. The composition of claim 5, wherein said polypeptide is selected from the group consisting of  $\alpha$ -globin,  $\beta$ -globin,  $\gamma$ -globin, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15,  $\beta$ -interferon,  $\gamma$ -interferon, cytosine deaminase, adenosine deaminase,  $\beta$ -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerbosidase, glucose-6-phosphatase, thymidine kinase, lysosomal glucosidase, growth hormone, nerve growth factor, insulin, adrenocorticotropic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor, thyroid stimulating

- 224 -

hormone of CFTR, EGFR, VEGFR, IL-2 receptor, estrogen receptor, Bax, Bak, Bcl-X<sub>s</sub>, Bik, Bid, Bad, Harakiri, Ad E1B, an ICE-CED3 protease neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), retinoblastoma, insulin, mast cell growth factor, p53, p16, p21, MMAC1, p73, zac1 and BRCA1.

- 5
8. The composition of claim 6, wherein said antisense construct is complementary to a segment of an oncogene.
9. The composition of claim 8, wherein said oncogene is selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *tk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.
- 10
10. The composition of claim 4, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β-actin, human globin α, human globin β and human globin γ promoter.
- 15
11. The composition of claim 1, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.
12. The composition of claim 1, wherein said composition further comprises one or more lipoproteins selected from the group consisting of apoA1, apoA-II, apoA-IV, acat, apoE, apoC-II, apoC-III and apo-D.
- 20
13. The composition of claim 11, wherein said apoB100 is selected from the group consisting of human, rat and baboon apoB100.
- 25
14. The composition of claim 1, wherein said polypeptide comprises at least two nucleic acid binding domains.
15. The composition of claim 14, wherein said nucleic acid binding domain contains a motif selected from the group consisting of a proline pipe helix DNA binding motif, a
- 30

- 225 -

ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motif and a nucleotide (ATP)-binding motif.

16. The composition of claim 14, wherein said binding domain is selected from the group consisting of SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, , SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166 and SEQ ID NO:175.
- 10
17. The composition of claim 1, wherein said polypeptide further comprises at least one nuclear localization sequence.
- 15
- 20 18. The composition of claim 17, wherein said nuclear localization sequence is from apoB100.
- 25
19. The composition of claim 17, wherein said nuclear localization sequence is selected from the group consisting of SEQ ID NO:178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210.
- 30
20. A method for expressing a polypeptide in a human cell comprising:

- 226 -

- (a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) a nucleic acid comprising an expression cassette comprising a sequence encoding said polypeptide and a promoter active in eukaryotic cells, wherein said coding sequence is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;
  - b) contacting said composition with said cell under conditions permitting transfer of said composition into said cell; and
  - c) culturing said cell under conditions permitting the expression of said polypeptide.

21. The method of claim 20, wherein said polypeptide is a tumor suppressor.

22. The method of claim 20, wherein said polypeptide is a cytokine.

23. The method of claim 20, wherein said polypeptide is an enzyme.

24. The method of claim 20, wherein said polypeptide is a hormone.

20 25. The method of claim 20, wherein said polypeptide is a receptor.

26. The method of claim 20, wherein said polypeptide is an inducer of apoptosis.

27. The method of claim 21, wherein said tumor suppressor is selected from the group consisting of p53, p16, p21, MMAC1, p73, zac1, BRCA1 and Rb.

28. The method of claim 22, wherein said cytokine is selected from the group consisting of IL-2, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, TNF, GMCSF,  $\beta$ -interferon and  $\gamma$ -interferon.

- 227 -

29. The method of claim 23, wherein said enzyme is selected from the group consisting of cytosine deaminase, adenosine deaminase,  $\beta$ -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerbrosidase, glucose-6-phosphatase, thymidine kinase and lysosomal glucosidase.

5

30. The method of claim 24, wherein said hormone is selected from the group consisting of growth hormone, nerve growth factor, insulin, adrenocorticotropic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor and thyroid stimulating hormone.

10

31. The method of claim 25, wherein said receptor is selected from the group consisting of CFTR, EGFR, VEGFR, IL-2 receptor and the estrogen receptor.

- 15 32. The method of claim 26, wherein said inducer of apoptosis is selected from the group consisting of Bax, Bak, Bcl-X<sub>s</sub>, Bik, Bid, Bad, Harakiri, Ad E1B and an ICE-CED3 protease.

- 20 33. The method of claim 20, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV tk,  $\beta$ -actin, human globin  $\alpha$ , human globin  $\beta$  and human globin  $\gamma$  promoter.

34. The method of claim 20, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.

- 25 35. The method of claim 20, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density apoB100.

- 30 36. The method of claim 27, wherein said binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.

37. The method of claim 20, wherein said polypeptide further comprises at least one nuclear localization sequence.
- 5      38. The method of claim 37, wherein said nuclear localization sequence is an apoB100 nuclear localization sequence.
39. The method of claim 20, wherein said polypeptide is selected from the group consisting of  $\alpha$ -globin,  $\beta$ -globin,  $\gamma$ -globin, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), mast cell growth factor.
- 10     40. A method for providing an expression construct to a human cell comprising:
  - (a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;
  - (b) contacting said composition with said cell under conditions permitting transfer of said composition into said cell; and
  - 20     (c) culturing said cell under conditions permitting the expression of said expression region.
41. The method of claim 40, wherein said expression construct comprises an antisense construct.
- 25     42. The method of claim 40, wherein said antisense construct is derived from an oncogene.
43. The method of claim 42, wherein said oncogene is selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.

- 229 -

44. The method of claim 40, wherein said expression construct comprises a nucleic acid coding for a gene.
45. The method of claim 44, wherein said gene encodes a polypeptide.
- 5 46. The method of claim 40, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV tk,  $\beta$ -actin, human globin  $\alpha$ , human globin  $\beta$  and human globin  $\gamma$  promoter.
- 10 47. The method of claim 40, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.
48. The method of claim 47, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density apoB100.
- 15 49. The method of claim 48, wherein said DNA binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.
- 20 50. The method of claim 40, wherein said polypeptide further comprises at least one nuclear localization sequence.
51. The method of claim 50, wherein said nuclear localization sequence is an apoB100 nuclear localization sequence.
- 25 52. The method of claim 40, wherein said gene encodes a polypeptide selected from the group consisting of  $\alpha$ -globin,  $\beta$ -globin,  $\gamma$ -globin, green fluorescent protein, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), mast cell growth factor.

- 230 -

53. A method for treating a human disease comprising:
- a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL; and
  - b) administering said composition to a human subject having said disease under conditions permitting transfer of said composition into cells of said human subject.
- 5 10
54. The method of claim 53, wherein said disease is selected from the group consisting of cancer, diabetes, cystic fibrosis and arteriosclerosis.
- 15 55. The method of claim 53, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*,  $\beta$ -actin, human globin  $\alpha$ , human globin  $\beta$  and human globin  $\gamma$  promoter.
- 20 56. The method of claim 53, wherein said nucleic acid binding domain is an apoB100 binding domain.
57. The method of claim 56, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density lipoprotein apoB100.
- 25 58. The method of claim 53, wherein said polypeptide comprises at least two nucleic acid binding regions.
- 30 59. The method of claim 58, wherein said binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 $\gamma$ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.

60. The method of claim 53, wherein said polypeptide comprises at least one nuclear localization sequence.
- 5 61. The method of claims 60, wherein said nuclear localization sequence is an apoB100 nuclear localization sequence.
62. The method of claim 53, wherein said nucleic acid encodes a gene.
- 10 63. The method of claim 53, wherein said expression construct comprises an antisense construct.
64. A pharmaceutical composition comprising:  
(a) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and  
15 (b) a nucleic acid comprising an LDL or VLDL binding sequence, wherein said nucleic acid is bound to said polypeptide;  
said pharmaceutical composition being dispersed in a suitable diluent.
- 20 65. A method of transforming a cell comprising:  
a) providing a cell;  
b) contacting said cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;  
25 wherein expression of said expression region is indicative of said transformation.
- 30 66. A method of transfecting a cell comprising the steps of:  
a) providing a cell;

- 232 -

- b) contacting said cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL; and
- 5 wherein expression of said expression region is indicative of said transfection.

## 1: The Amino Acid Sequence of Apo B-100

<p>10            20            30            40            50            60            70            80            90</p> <p>EEEMLENVSLVCPKDATRFKHLRKYTYNAYEAESSSGVPGTADRSATRINCKVELEV PQLCSFJLKTSQCTI.KEVYGFNP EKGALLKKTKNSEEFAAAMS  RYELKLAIPEGKQVFLYPEKEDEPTYILNIKRGIIISALLVPPETEEAQWQLFLDTVYGNCS THFTVKTRKGIVATEISTERDLGQCDRFKPIRTGISPLAI  IKGMTRPLSTLISSSQSCQYTLDAKRKHVAEAI CKEQHFLLPFSYNKNGMVAQVTQTLKLEDTPKINSRFFGE GTKMGLA FESTKSTSPKQAEAVLK  TQELKLTLISEQNIQRANLFNKL VTELRLGLSDEAVTSLLPQLIEVSSPITLQALVQCGQPQCS THILQWLKRVHANPLLIDVVVTYLVALIPEPSAQQLR  E1FMARDQSRATL YALSHAVNNYHK TNPTGTQELLDIANYLMEQIQDDCTGDEDYTYL ILRIVIGNMGTQMEOQ TPELKSSILKCVQSTKPSLMIQKAA  IQALRKMEPKDKDQEVL LQTFLLDASPGDKRLAAYMLMRSPLSPSQA DINKIVQILPWEQVNKFVASHIANILNSEEELDIQDLKL VKEALKESSQLPTV  MDFRKF SRNYQLYKVSVSLPSSLDPASAKIEGML IFDPNNYL PKE SMLKTTL TA FGFA SADLIEIGLEGKGFEPTEALFGKQGFFFDSVNKA LYVWNQVP  DGVS KVLVDHF GYTKDDKHEDDMVNGIMLSVEKL IKDLKSKEVPEARAYLRILGEELGFASLHDLOQLGKLLMGARTL QGIPQMIGEVIRKGSKNDFFL  HYIFMENAFELPTGAGLQLQI SSSGVIA PAKAGVKLEVANM QAEVAKPSVSVEFVTNMGI IIPDFARSGVQMNTNFHE SGLEAHVALKAGKLKF IIP  SPKRVKLLSGGNLTLLHVSTTKTEVPIPLIENRQSW SVCKQVFPGLN YCTSGAYSMASSTDASYYPL TGDRLEELRPTGEIEQYSVSATYELQREDR 1000</p>	<p>10            20            30            40            50            60            70            80            90</p> <p>ALVDTLK FVTQAE GAKQTEATMTFKYNRQSMTLSSEVQIPDFDV DLT I RVNDESTE GKT SYRL TLDI QNKKITEVAL MGHLSCDTKEER KIKGVISIP  RLQAE ARSEILAHWSPAKLLLQMDSSATAYGSTS VSKRAVWHYDEEKIEFEWNTGTNVD TKKMTSNFPVDSLSDYPKSLHMYANRLLDHRYPETDMTFRHVG  SKLIVAMSSWLQKASGSLPYQTQLQDHINSLKEFNLQNMGLPDFHIPENLFLKSDGRVKYTLNKNSLKIEIPLPFGGKSSRDLKMLETVRTPALHFKSVG  FHLP SREFQVPTFTIPKL YQLQVPLLGVLDSLTVWYSNLYNWSASYSGGNTSTDHFSLRARYHMKADSVV DLLSYNVQSGETTYDHKNTFTLSCDGSLR  HKFLDSNIKFSHVEKLGNNPVSKGLLIFDASS SWGPOMSAVHLDSSKKQHFLVKIDGQFRVSSFYAKGTYGLSCQRDPNTGRLNGESNLRFNSSYL  QGTNQIITGRYEDGTLSLTSTS DQLQSGI IKNTASLKYENYEL TLKSDTNGKYNFATSNKMDMTFSKQN ALLRSEYQADYESLRFSSL SGSLNSHGLELN  ADILGTDKINSGA HKATL RIGQDGIST SATTNLKCSLVL ENEL NAEGLSGASMKLT TNGR FRENNAKFSLDGKA NLTELSLGSAYQAMILGVDSK NIF  NFKVSQ EGLKL SN DMMG S YAE MKFDHT NSL NIAGL SLD FSSK LD NJYSSD KFYQ T VNL QLQ PYSLVTTLNSDLKYN ALDL TN NGKL RL EPLKLHVAGNL  KGAYQNEIKHIYAISSA ALSAS YKADTVAKVQGV FSHRLN TDIA GLAS AID M S T NYNS DSL HFSNVFRSVMAPFTMTIDAHTNGKL ALWGEHTGQL  YSKFLKKAPEPLAFTFSHDYKGSTSHHL VSRKSISAAL EH KV S ALL TPAE Q TGT WKL KTOFNN NEY S QD L DAY NT KDKIGVEL T GRT L ADL TLD SPIK VP 2000</p>
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**FIG. 1A**

2/56

10	20	30	40	50	60	70	80	90	
LLLSEPINIIDALEMRAVEKPKQEFTIVAFVKYDKNQDVHSINLPFFETLQEYFERNRQTIIWVENVQRNLKHINIDOFVRKYRAALGKLPOQANDYLN SFNWEROVSHAKEKLTALTKYRITENDIQIALDDAK1INFNEKLSQLQTYMIQFDQYIKDSYDQLQQLQQLKQLQQLKQLQQLKQLQQLKQLQQL DLHIFTENIDFNKSGSSTSASWIQNVDTKYQIRIQCQKLSQLQTYMIQFDQYIKDSYDQLQQLKQLQQLKQLQQLKQLQQLKQLQQLKQLQQL FEVAEKINAFAKVKHELIERYEVDQQIQWLMDKLVELTHQYKLETTIQQLSNVLQQVKIKDYFEKLVGFIIDAVKKNLSFKTFIEDVNKFQDFMLIKKL KSFDYHQFVDETNDKIREVTQRNLNGEIQALELPKQAEALKLFLEETKATVAVYLESQDTKITLIIINWLQEALSSASLAHMKAKFRETELDTRDRMYDMO 1QQFLQRYLSSLVGQVYSTLVITYISDWNTLAACNLTDFAEQYS1QDWAKRMKALVEQGFTVPEIKTILGTMPAFEVSLQALOKATQTPDFIVPLTDLRIP SVQINFKDKNIKIPSRFSFTPEFTILNTFHIPSFTIDFVEMKVKIIRTIDQMQNSELQWPVPDIYLRLDKVEDIPLARTLPDFRPIIAIPEFIIPTLN LNDFOVQPDLIPEFQLPHISHTIEVPTFGKLYSILKJQSPLFTLDANADINGGTTSANEAAGIAASI1TAKGESEKLEVLFNDFQANAQLSNPKINPLAKES VKFSSSKYLRTEHGSEMLFFGNAIEGKSNTVASLHTEKTNLELSNGVIVKINNQLTLDNTNKYFHLNIPKLDSSQADLRNEIKTLLKAGHIAWTSSGKG SWKWAQPFRFSDEGTHEQSISFTIEGPLTSFGLSNKINSKHLRWNQNLVYESGSLNFSKLEIQSQVDSQHVGHSQLTAKGMALFGECKAFTGRHD AHLNG 3000	10	20	30	40	50	60	70	80	90
KVIGTLKNSLFFSAQPFEITASTNNNEGNLKVRFPRLTGKIDFLNNYALFLSPSAQQASWQVSARFNQYKYNQNF SAGNNENIMEAHVGINGEANLDFLN IPLTIPEMRLPYTIIITPPPLKDFSLWEKTRGLKEFLKTTKQSFDSLVKQAQYKKNKRHSITNPLAVLCEF1SQS1KSFDRRHF EKNRNNALDFVTKSYNETK IKFDKYKAEKSHDELPRTFQIIPGYTVPVWNVESPFTIEMSAFGYVFPKAVSMPFSFSLGSDVRPSYTLII.PSLELPVLHVRPNKLSLPHFKELCTIS HIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLLSSSSVIDALQYKLEGTRLTRKRGKLATAI.SLSNKFVEGSHNSTVSLTTKNMEVSAVK TTKAEIPILRMNFQEELNGNTKSKPTVSSMFEKYDFNSSMLYSTAKGAVDJKLSELSLTSYFSIESSTKGDVKGSVLSREYSGTIASEANTYNSKSTR SSVKLQGTISKIDDIWNL'VEKENFAGEATLQRISLWEHSTKNNHQLEGLFTNGEHTSKATLESPWOMSALVQVHASQPSFFHDGPDLGQEVALNANTK NQKIRWKNEVRIHGSFQSQVELSNDQEKAHLDIAGSLEGHLRFLKNIIPVYDKSLWDFLKLDVTTSIGRRQHLRVSTAFVYTKNPNGYSFSIPVKVLA DKFITPGKLNDLNSVLVMPTFHVPFTDQVPSCKLDFREIQIYKKLRTSFAFLNPLTLPKVPEVDVLTKYSQFEDSLIPFFELTVPESQLTVSQFTL PKSVSDGIAALDLNAVANKIADFELPTIIVPEQTIEIPS1KFSPVNAWTSASLKNKADYVETVLDSTCSSTVQFLEYE 3900 LNLGLTHKIEDGTLASKTKGTLAHRDFSAEYEDGKFEGLQEWEGKAHLNIKSPAFTDLHLRYQDKKGISTSAAASPAVGTVGMDMDEDFFSKWNFYY 4000									

**FIG. 1B**

3/56

PQSSPDKLTIFKTELRVRESEETQIKVNWEEEAASGLLTSLLKDNPVKATGVLYDVVNKYHWEHTGLTLREVSSKLRRNLQNNAEWYQGAIRQIDDID  
VRFQKAASGTTGTYQEWKDKAQNLYQELLTOEGQASFQGLKDNPVFDGLVRVTQKFHMVKHLIDSЛИDFLNFPRFQFPGKPGIYTREELCTMFIREVGV  
LSQVYSKWHNGSEILFSYFQDLVITLPFELRKHLIDVISMYRELKDLISKEAQEVFKAIQSLKTTTEVLRNLDLLQFIQLIEDNIKQLKEMKFTYLIN  
YIQDEINTIFNDYIPYVFKLKENLCNLHKFNEFIQNELQEAQELQQIHQYIMALREEYFDPSIVGWTWKKYELEEKIVSLJKNLLVALKDFHSEYIV  
SASNFTSQLSSQVEQLHRN1QEYLSILTDPDGKGEKIAELSATAQEIKSQAIATKKIISDHYHQQFRYKLQDFSDQLSDYYEKFIAESKRIDLISQN  
YHTFLIYITELLKKLQSTTVMNPYMKLAPGELTIL

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

	10	20	30	40	50	60	
B1	KYTNYEA--ESSGVPGTADSR-SATRINCKVELEVQLCSFILKTSQ						(SEQ ID NO:3)
R9	AYDFNYPPIKKDSSSQLL-SVQQGETIYILN-KNSSGWWDG--LVIDDNN						(SEQ ID NO:4)
	Y***NY * *SSS ** *** * * N K *** *** S*						55%
B2	VYGFNPEGKALLKKTKNSEEFAAMSRYELKLAYPEGKQV -FL YPE						(SEQ ID NO:5)
R33	LYDFVASGDNTLSITKGEKLRLVLYNHNGEWCEAQTKNGQQGVPSN						(SEQ ID NO:6)
	*Y F * G L TK **** *Y* * *** K* *** *						51%
B3-1	FLPFSYNNKYGMVAQVTQTLKLEDTPKINSRFF-GE-GTKKMGLAF						(SEQ ID NO:7)
R35	LFDYKAQREDELT -FTKSAIQVNFVKQEGGMWRRGYGGKKQ-LWF						(SEQ ID NO:8)
	** * *** * *T *** *** K * *** G* G KK L*F						54%
B3-2	FLPFSYNN-KYG-MVAQVTQTLKL -EDTPKINSRFF -GE GTKKM---GLA-FE						(SEQ ID NO:9)
R18	LH - SYEP SHDGLGFEKGEQLRILEQSGE ---MWKAQ-SLTTGQEGFIPFN						(SEQ ID NO:10)
	* SY* * G *** * L** E** *** *** G* F*						51%

FIG. 2A

5/56

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

B4	YTYLILRIVIGNMGQTMEQLTPEL-KSSILKCVQSTKPSLMIQKAAIQALRKMEPKDKD--QEVL	(SEQ ID NO:11)
R52	VVALFD-YAA-VNDR-DL--QVLKGE-K-LQWLRLSTG--DWMLARSLVTG--REGYVPSNFWAP	(SEQ ID NO:12)
	* *L* *** * * *L ** K *Q * * *L **** *L ** * **V**	50%
B5	AFGFASADLIEIGLEGKGFPEPTLEALFGKQGFFPDS-VN-KALYWVNGQVPD	(SEQ ID NO:13)
R34	LYDFAAENPDELTFNEGAVVTVINKSNP-D-MW-EGELNGQRGVFPAS--YVE	(SEQ ID NO:14)
	***FA* ** E* ** ** * * * *N **** * * **	59%
B8	FGYTKDDKHEQ-DMVNGIMLSVEK--LIKDLKSK--EV-PEARAYLRILGEE	(SEQ ID NO:15)
R25	YDYKKEE--EDIDLHLGDLITVNKGSLVALGFSDGQEAKPPEIGGLNGY-NE	(SEQ ID NO:16)
	* Y K** E* D* G ***V*K L** S E* PE **L * *E	56%
B8	FDYHQFVDETNDK-IREVTQRLNGEIQ-ALELPQKAELKLFLEETKAT-V-AVYL	(SEQ ID NO:17)
R32	YDY-----QEKS PREV TMKK-GDILTLNINSTNK-DMWKVEVND-RQGFVPAAYV	(SEQ ID NO:18)
	*DY ***K *REV T * G*I *L* *K ***K* *** * V A*Y*	52%

FIG. 2B

B9-1	YDM--DIQQELQRYLSSLVGQVYSTLVTYISDNWT--LAAK-NLTDFAEQYSIQDWA	(SEQ ID NO:19)	
R35-2	FDYKAQREDELTFKSAIIQNVEKQDGG--MWRGDDGKKQLW-FPSNY-VEEMI	(SEQ ID NO:20)	
	*** * **EL S** Q *	WW ***K *L F* *Y *****	54%
B9-2	YDMDIQ---QELQRYLSSLVGQVYSTLVTYISDNWTLAAKNL TDFAEQ-YSIQDWA KRMK	(SEQ ID NO:21)	
R43	IQ-DYEPRLTDEI-RI-SL-GEVKV-ILATHTDGMCLVEKCNTRKGTIHVSVDD--KRYL	(SEQ ID NO:22)	
	*Q D** *E* R* SL G* * *** *D W L* K T * *S**D KR*		57%
B9-1	YQMDI -QQELQ -R YLSLVGQVYSTLVTYIS-DW -TLAA-KNLTDFAEQYSIQDW A	(SEQ ID NO:23)	
R49	YDYEARTEDDL TFTK -----GEKF-HILNNTEGDWWEARSLSSGK--T-G-CIPSNYVA		
	Y*** * **L * G* * ** DW *L** K T * * *A		51%
B10	TYDFSFK--SS-VITLNTNAE-LFNQSDIVAHLLSSSSVIDALQY-----KLE	(SEQ ID NO:24)	
R9-2	DNYPIKKDSSSQLSVQ-QGETIY----ILNK--NSS-GWWMDGLVIDDSNGKV N	(SEQ ID NO:25)	
	DF ** K SS *** * **E ** I* * SS * *D*L * K**		56%
B11	KYDFNSSMLYSTAKGAVDHKLSESLTS-----YFSIESSTKGDVGSVLSRE Y	(SEQ ID NO:26)	
R47	EPYVAIK-AYTAVEGDEVSLLEGAEVVIHKLLDGWWVIR---KDDVTGYFPMYL	(SEQ ID NO:27)	
	* * *Y** G L E** ** I K DV G **S *		50%

**FIG. 2C**

7/56

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

B12	LWDFLKLD-----VTTSIGRRQHLRVSTA-----FVYTKNPNGYSFSIPVKVLADKFITPGLKL	(SEQ ID NO:28)
R3	LYDF-KAEKADELTTYVG--ENL-FICAHHNCEWFIAK-PIGRGGPGL-VPVG-FVSI-IDI	(SEQ ID NO:29)
	L*DF K** *TT *G * L * A ***K P G * * V** F*** *	54%
B13	VLYDYVWKY-HWEHTGTL-LR-EVSSK-LRRNLQNNMAEWVYQGAIRQIDDI	(SEQ ID NO:30)
R3-2	VLYDF--KAEKADE--LTTYVGENLFCIAHHN---CEWFI--AKPIGR	(SEQ ID NO:31)
	VLYD* K* *** LT * E ***N EW** *** I *	51%
B14	KPGIY--TREEELCTMFIREVGTVL-----SQVYSKVHNGSE--ILF-SYFQ--DL	(SEQ ID NO:32)
R36	LFGFVPETKHEELQ-VMPGNIVFVLKKGNDNWATVM--F-NG-QKGLVPCNYLEPVEL	(SEQ ID NO:33)
	**G* *T*EEL *** ** VL * V* * NG * *** *Y** *L	56%
B15	GKPGIYTREEELCTMFIREVGTVLSQL-----VYSKVHNGS-E--ILFS-YFQ--D	(SEQ ID NO:34)
R59	AKFDYVAQQEQE LDIKKNERLWLDDSKSWW-RVRN-SMNKTGFVPSNYVERKN	(SEQ ID NO:35)
	*K* *** *E * I* ** *V*N S * ***S Y** *	53%

FIG. 2D

8/56

Identification of the regions of apo B-100 and the proteins compared in Figures 2A-2D.

Reference Protein Name:	<u>SEQ ID NO.</u>
Apo B-100 region B1 (aa 24-69)	SEQ ID NO:3
r9 (aa 66-114). cell division control protein 25 gim 4857	SEQ ID NO:4
Apo B-100 region B2 (aa 75-119)	SEQ ID NO:5
r33 (aa 69-114). Ab1 proto-oncogene tyrosine kinase (P150) gim 13887	SEQ ID NO:6
Apo B-100 region B3-1 (aa 240-283)	SEQ ID NO:7
r35 (aa 799-841). 1- Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma (PLC-gamma. PLC-II) gim 18895	SEQ ID NO:8
Apo B-100 region B3-2 (aa 240-284)	SEQ ID NO:9
r18 (aa 69-114). Lck proto-oncogene tyrosine kinase (P56-LCK) gim 14213	SEQ ID NO:10
Apo B-100 region B4 (aa 457-518)	SEQ ID NO:11
r52 (aa 57-109). BLK protein tyrosine kinase (B lymphocyte kinase) (P55-BLK) gim 13991.	SEQ ID NO:12
Apo B-100 region B5 (aa 652-700)	SEQ ID NO:13
r34 (aa 984-1031). Myosin IC heavy chain gim 16466	SEQ ID NO:14
Apo B-100 region B6 (aa 711-756)	SEQ ID NO:15
r25 (aa 12-61). Phosphatidylinositol 3-OH gim 18072	SEQ ID NO:16

FIG. 2E

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9/56

Identification of the regions of apo B-100 and the proteins compared in Figures 2A-2D.

Apo B-100 region B9-1 (aa 2497-2547)	SEQ ID NO:19
r35-2 (aa 800-850). 1- Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma. (PLC-gamma. PLC-II) gim 18895	SEQ ID NO:20
Apo B-100 region B9-2 (aa 2497-2551)	SEQ ID NO:21
r43 (aa 444-496). nuclear fusion protein FUS1 gim 9498	SEQ ID NO:22
r49 (aa 86-134). Fgr Proto-oncogene Tyrosine gim 14097	SEQ ID NO:23
Apo B-100 region B10 (aa 3311-3355)	SEQ ID NO:24
r9-2 (aa 66-114). Cell division control protein 25 gim 4857	SEQ ID NO:25
Apo B-100 region B11 (aa 3434-3482)	SEQ ID NO:26
r47 (aa 229-280). Neutrophil Cytosol Factor 1 (NCF-47K) gim 16659	SEQ ID NO:27
APO B-100 region B12 (aa 3657-3710)	SEQ ID NO:28
r3 (aa 162-201)Bem-1 protein gim 3905	SEQ ID NO:29
Apo B-100 region B13 (aa 4053-4099)	SEQ ID NO:30
r3-2 (aa 163-214)Bem-1 protein gim 3905	SEQ ID NO:31
Apo B-100 region B14 (aa 4180-4222)	SEQ ID NO:32
r36 (aa 248-299). Neutrophil NADPH oxidase factor (P67-PHOX) gim 16660	SEQ ID NO:33
Apo B-100 region B15 (aa 4179-422)	SEQ ID NO:34
r59. Cytoplasmic protein gim 16669	SEQ ID NO:35

FIG. 2F

10/56

Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

9.	WYHASLTRAQAEHMLMRV -	PRDGA-FLVRKRNEPNSAISFR-AEGKIKH	
10.	FFGEG-TK -	-----KMGLAFESTKSPPKQ-AEAVLTKLQELKKLTISEQNIQ-RANL ** T* *M * * P** A *** *F* ***S **	
9.	C-RVQQEGTVMLGNSEFDSLVDLISYYEKHPL	-----YRKMKLK	(SEQ ID NO:36)
10.	FNKLVTELRGSLDEAVT-SLLPQLIEVSSPITLQALVQCGOPCSTHILQMLKRVHAN ** E * ** SL* *LI * L	-----	(SEQ ID NO:37) 4
		*****	
5.	WFHG -	KISKQEAYNLLMTVGQACSFVLVRPS-DNTPGDY-SLYFRTSEN QRFKICP	
11.	IMLSWEKLIKDLKSKE -	VPEAR-AYLRLI <u>G</u> EEL-G-FASLHDLQLLGKLLMGAR ** K* K* V *A ***R* ** G * SL *	
5.	T-----PNINQFMGGRRYYN-SSIGDIIDHYRK-EQIVEGYY-LKEP	-----	(SEQ ID NO:38)
11.	TLQGIPQ--MIGE-VIRKGSKNDFLHYIFMENAFELPTGAGLQL T p* M*G ** S D** HY E***E *	-----	(SEQ ID NO:39) 4
		***	

11/56

Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

5.	WF <u>HGKIS</u> -- <u>KQEAYNLLMTVGQACSF</u> L_VRPSDNTPGDYSLYFRTSEN <u>IQ</u> -- <u>R</u> --F		
16.	YFH-K <u>LNIPK</u> --LD--FSS-QAD--LR--NEIK <u>I</u> --TLL-KAGH <u>I</u> AWTSSG <u>KGSW</u>		
	*FH K* K ** ** QA *R ** *L* ** * * *		(SEQ ID NO:40)
5.	<u>KI</u> -CPTPNQNQFMMG <u>G</u> RYNNSSIG <u>D</u> II <u>D</u> H <u>YRKE</u> QIVE <u>E</u> GY <u>YLK</u>		(SEQ ID NO:41)
16.	K <u>WACPRFSD</u> E-- <u>GTH</u> --ESQISFT <u>TIE</u> G <u>P</u> LTSF <u>G</u> LSN <u>KINS</u>		
	K* CP * ** G * *S I I* * * *		
6.	WYW <u>GDISR</u> --EEVNE--- <u>KL</u> RDT <u>PDGTFL</u> VR <u>DASSK</u> I <u>QG</u> --DY <u>TL</u> TL <u>RKG</u> NN <u>NKL</u>		
17.	<u>FFSAQPFEITASTNNEGNLKVR</u> -- <u>FPLR</u> -LT <u>GKIDFLNNYALFLSPSAQQAS</u>		
	** *** NE K* <u>R</u> F** <u>R</u> ** K <u>I</u> * *Y* <u>L</u> L ***		(SEQ ID NO:42)
6.	<u>IKVFHR</u> --DG <u>KYG</u> --FSEPLTFC <u>SVVDL</u> I <u>THYRHE</u> SLAQYN <u>NAKLDTRLLYPVSKY</u>		
17.	W <u>QVSARFNQYKYNQNFSA</u> GNNEN-IM <u>EA</u> -- <u>HVGINGEANLD</u> F-LN <u>IPLTIPEMRL</u>		(SEQ ID NO:43)
	* V <u>R</u> * <u>KY</u> FS **E* H* * A*** L** L *p **		

Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

8.	WF <u>HGKL</u> GAG-RDGRHIAERLLTEYC <b>IETGAPDG</b> SFLV <u>R</u> ESETFVG <b>D</b> -YTL <u>SFWRNG</u> <b>K</b>	
21.	FP- <u>GKPGIY</u> TRE-----ELC-----TMFIRE <u>WGT</u> VLSQVYSK <u>S</u> --V <u>HNGS</u>	
8.	** GK*G* R* E*C ***RE T** * Y* **NG	(SEQ ID NO:44)
21.	VQ <u>HCRHSR</u> DAGTP <u>KFFL</u> TDNL-VFD--SL <u>Y-DL</u> I <u>TH</u> -----YQQVPLRCNE <u>FEMRL</u> SE -EILFSYF-QDLVITLP <u>FELRKHKL</u> IDVIS <u>M</u> Y <u>R</u> ELL-K <u>DLSKEA</u> QEV-F <u>KA</u> I <u>QS-L</u> K <u>TTE</u>	(SEQ ID NO:45)
	* QD* *F **D S*Y *L* * Q*v ** * ** *E	

Structurally important motifs are indicated by double underline. Percent similarity is right.

FIG. 3C

Identification of the reference proteins as well as the apoB-100 regions used in the above alignments

<u>Reference Protein Name:</u>	<u>Sequence ID No.</u>
9. = phospholipase Cyl. Residues 668-753	SEQ ID NO:36
10. = Apo B-100 region 10. aa(271-377)	SEQ ID NO:37
5. = GTPASE-activating protein (GAP) (RAS P21 PROTEIN ACTIVATOR). Residues 348-437	SEQ ID NO:38
11. = Apo B-100 region 11. aa(727-819)	SEQ ID NO:39
5. GTPASE-activating protein (GAP) (RAS P21 PROTEIN ACTIVATOR). Residues 348-435	SEQ ID NO:40
16. = Apo B-100 region 16. aa(2861-2938)	SEQ ID NO:41
6. = p85 $\alpha$ . Residues 326-424	SEQ ID NO:42
17. = Apo B-100 region 17. aa(3011-3110)	SEQ ID NO:43
8. = phospholipase Cyl. Residues 550-655	SEQ ID NO:44
21. = Apo B-100 region 11. aa(4177-4267)	SEQ ID NO:45

FIG. 3D

**Comparison of the Apo B-100 SH1-like Region to SH1 Kinase Domains  
Known Signal Transduction Proteins.**

	10	20	30	40	50	60	
	V G * **	N*	VA <u>K</u> *	P T*	VPE	*E*	*K *
							*V *
APOB	VSDGIAALDL	-----NA-----VANK-IADFELP-TIIVPEQTI-EIPSIK-FSVPAGIVIPSF					
SRC	LGQQCFG-EVW <sup>MG</sup> -TWING-T-- <u>T</u> RVAI <u>K</u> TL <u>K</u> -----PGTMS-PEAFLQEAQVMKKLRH-EKLV----						
CFYN	LGNGQFG-EVW <sup>MG</sup> -TWINGNT-- <u>T</u> KVA <u>I</u> KL <u>K</u> -----PGTMS-PESFLEAQIMKKLKH-DKLV----						
HCK	LGAGQFG-EVW <sup>MA</sup> -TYN-- <u>K</u> HTKVAVK <u>T</u> M <u>K</u> -----PGSMSV-EAFLAEANV <u>M</u> KTL <u>Q</u> H-DKLVK <u>L</u> H-						
LYN	LGAGQFG-EVW <sup>MGY</sup> -YN-NS-- <u>T</u> KVAVK <u>T</u> TL <u>K</u> -----PGTMSV-QAFLEEANL <u>M</u> KTL <u>Q</u> H-DKLVR <u>L</u> -Y						
LCK	LGAGQFG-EVW <sup>MGY</sup> -YNG-- <u>H</u> TKVAV <u>K</u> SL <u>K</u> Q-----GSMS-PDAFLAEANL <u>M</u> K <u>Q</u> L <u>Q</u> H-QRLV <u>R</u> L-Y						
	70	80	90	100	110	120	130
	**** * P*Y *T * * <u>K</u> *** *L *** * * *** * * *** * I *G						
APOB	QAL-TARFEVDSPVYNAT-WSASL <u>K</u> NKA <u>D</u> YVETV <u>L</u> --DSTCSSTV <u>Q</u> F <u>L</u> --EYELNV <u>G</u> TH <u>K</u> I <u>E</u> <u>G</u>						
SRC	Q-LY-A-WVSEEPYIYVTEY-MS <u>K</u> G-S-LLD-FL <u>K</u> GET-G <u>K</u> --YL <u>R</u> L <u>P</u> QL-VDMAAQ--IASG						
CFYN	Q-LY-A-WVSEEPYIYVTEY-MN <u>K</u> G-S-LLD-FL <u>K</u> D <u>G</u> EG-R <u>A</u> L--KL <u>P</u> N <u>L</u> -VDMAAQ--VAA <u>G</u>						
HCK	-AVVT-K---E-PIYIITEF-MA <u>K</u> G-S-LLD-FL <u>K</u> S <u>D</u> E-GSK <u>Q</u> P-L <u>P</u> KL----IDFSAQ--IAEG						
LYN	-AVVT-R---EEPIYIITEY-MA <u>K</u> G-S-LLD-FL <u>K</u> S <u>D</u> EGG-K <u>V</u> L-L <u>P</u> KL----IDFSAQ--IAEG						
LCK	-AVVT----QEP <sup>I</sup> YIITEY-MEN-G-S-LVD-FL <u>K</u> TPSGI-K-L <u>T</u> INK <u>L</u> --LDMAAQ--IAEG						

**FIG. 4A**

15/56

Identification of the Apo B-100 SH1-like Region and  
the SH1 Kinase Domains of Known Signal Transduction  
Proteins and Their Corresponding Sequence  
Identification Numbers

Reference Protein	Sequence ID No.
ApoB (aa 3804-4006)	SEQ ID NO:46
SRC (aa 275-488)	SEQ ID NO:47
FYN (275-488)	SEQ ID NO:48
HCK (268-480)	SEQ ID NO:49
LYN (252-469)	SEQ ID NO:50
LCK (250-462)	SEQ ID NO:51

FIG. 4B

The Inter-Kringle Proline-Rich Regions of Apo[a] are Compared to the Proline-Rich Region of SH3-Binding Protein 1 (3BP1).

3BP1 ikr2	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	-SDAEG-TAVAP <u>PPTVTPVPSLEAPSE</u> -QA---P <u>TEQR</u> -PGVQE	(SEQ ID NO:58)
3BP1 ikr3	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	-SDAEG-TAVAP <u>PPTTPIPSELAPSE</u> -QA---P <u>TEQR</u> -PGVQE	(SEQ ID NO:59)
3BP1 ikr4	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	-SDAEW-TAFVPP <u>NVILAPSLEAFFE</u> -QA---L-T <u>E</u> E-T <u>P<u>G</u>V<u>QD</u></u>	(SEQ ID NO:60)
3BP1 ikr5	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PP<u>V</u></u> --V <u>PPQQPARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	--L-V-T <u>E</u> --SSV <u>LATLTWVPD<u>PST</u></u> -EASSEEA <u>P<u>T</u>E<u>Q</u></u> -S <u>P<u>G</u>V<u>QD</u></u>	(SEQ ID NO:61)
3BP1 ikr7	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	P--VMESTLL <u>TTPTWVVP<u>STELP</u>SE</u> -EA---P <u>TEN</u> -ST <u>G</u> V <u>QD</u>	(SEQ ID NO:62)
3BP1 ikr8	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	P--VTESSV <u>LTTPTWVVP<u>STEAP</u>SE</u> -QA---P <u>P</u> -E-KSP <u>VV</u> QD	(SEQ ID NO:63)
3BP1 ikr9	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	-SETE--SGV <u>LET</u> --P <u>T</u> V <u>V</u> P-E-P <u>SM</u> -EAHSEA <u>A<u>P</u>T<u>E</u>Q</u> -T <u>P<u>V</u>V<u>R</u>Q</u>	(SEQ ID NO:64)
3BP1 ikr10	TS-LRAP <u>T</u> -M <u>PPP</u> -L <u>PPVPP</u> -Q-P <u>ARRQSRR</u> --L <u>P<u>A</u></u> --SPV <u>I<u>S</u></u>	(SEQ ID NO:57)
	-SDTESGT <u>WVAPPTV</u> --I---QV <u>P<u>SL</u></u> -----G <u>PP</u> SE <u>QD</u> -	(SEQ ID NO:65)

FIG. 5A

17/56

Identification of the Inter-Kringle Proline-Rich Regions  
of Apo[a] and the Proline-Rich Region of SH3-Binding  
Protein 1 (3BP1) compared in FIG. 5A.

Reference Protein	Sequence ID No.
3BP1	SEQ ID NO:57
Proline-Rich Region of Sh3-Binding protein 1	
ikr2 amino acids (106-141)	SEQ ID NO:58
ikr3 amino acids (3322-3357)	SEQ ID NO:59
ikr4 amino acids (3436-3471)	SEQ ID NO:60
ikr5 amino acids (3550-3585)	SEQ ID NO:61
ikr7 amino acids (3770-3805)	SEQ ID NO:62
ikr8 amino acids (3884-3919)	SEQ ID NO:63
ikr9 amino acids (3998-4033)	SEQ ID NO:64
ikr10 amino acids (4112-4137)	SEQ ID NO:65

FIG. 5B

18/56

## Proteins Are Compared to the Analogous Regions in Apo B-100.

	*K*A*** R* *** ** *G* G*** *	PGTAD - SRSATRI (SEQ ID NO:66)	PKDAS --- QRRSLEP - AENVHGA-GGGAFPASQTPSKP (SEQ ID NO:67)	DKEATKLTEERDGSLN---Q-SSSGYRYGT-DP---TPQHY (SEQ ID NO:68)
B100(13-49)				
SRC(7-40)				
FYN(7-38)				
apoB-100 (4448-4536)	*** * TF Y* *L * **T *P Y	PGE L	IQNYH-TFLIYITELLKKLQSTTVMN P-YMKLAPGE-LTII L (SEQ ID NO:69)	
SRC(505-535)	PEE-RPTF-EYLQAFLEDYFTST--EPQYQ---PGENL----	(SEQ ID NO:70)		
FYN(506-536)	PEE-RPTF-EYLQSFLLEDYFTAT--EPQYQ---PGENL----	(SEQ ID NO:71)		
HCK(498-526)	PEE-RPTF-EYIQSVLDDFYTAT--ESQYQQQ-P-----	(SEQ ID NO:72)		
LYN(483-511)	AEE-RPTF-DYLQSVLDDFYTAT--EGQYQQQ-P-----	(SEQ ID NO:73)		
LCK(480-508)	PED-RPTF-DYLRSVLEDFFTAT--EGQYQPQ-P-----	(SEQ ID NO:74)		

\*indicates conserved amino acids

FIG. 6

## Examples of Proline Pipe Helix Structures in ApoB-100

SEQ ID NO:	Sequence	Sequence Source
77	PQNAKLKIKRPVKVQPIARVWY	Tus proline pipe (223-243)
78	PDFRLPEIAIPEFIIPTLNND	ApoB-100 (2682-2702)
79	NDFQVPDLHIIPEFQLPHISHTI	ApoB-100 (2702-2723)
80	PSLELPVVLHVPRNLLKLSLPHFK	ApoB-100 (3273-3294)

FIG. 7

20/56

Sequence Comparison of DNA-Binding Protein ISGF3 $\gamma$  SEQ ID NO:81, and a Similar Region of Apo B-100 SEQ ID NO:82, Located Between Residues 0008 and 0393.

MAS--GRARCT--RKLRLNWVEQVESGQ--FPGWCDDTA-KTMFRI VSLVCPKDA-TRFKHLRKYTYN-YEAESSSGVPGTADSRSATRINCKV ** * T **LR * ** E* *PG *A *	ISGF3 $\gamma$ apoB100 ** *
PW--KHAGKQDFRESQDAAFFKAWAIF---KGKYK---EGDKEVPER ELEVPPQLCSFILKTSQCTL--KEVYGFNPEGKALLKKTKNSEEEFAAM * * ** SQ ** K ** F K* *K * * * **	ISGF3 $\gamma$ apoB100 * *
GRMDVAEPYKVYQLLPPG-IVSGQPGTQKV-PS----KRQHSSVSSE SRYE---LKL--AIPEGKQWFLYP--EKDEPTYILNIKRGIIISALLV R** *KV * *P G V P *K* p* KR S*	ISGF3 $\gamma$ apoB100 * *
RKE-EDAMQNCTLSPSVLQDSLNNEGASGGAVHSDIGSSSSSSPEP PPETEEAKQVL-FLDTVYGNCSHTVKTTRKGNVATEISTERDLGQCD E E*A Q * *V* * * * * S*	ISGF3 $\gamma$ apoB100 * *
QEVTDTTEAPFGDQRSLEFLLPPEPDYSLLLTFIYNGRVVGAEAQVQS RFKPIRTGISPLAIKGMTTRPLSTLISSSQSCQYTLD <del>AKRKHVAE</del> IC T * * * * L * S * * *** A**	ISGF3 $\gamma$ apoB100 * *

FIG. 8A

Sequence Comparison of DNA-Binding Protein ISGF3 $\gamma$  SEQ ID NO:81, and a Similar Region of Apo B-100 SEQ ID NO:82, Located Between Residues 0008 and 0393.

<b>ISGF3<math>\gamma</math></b> <b>apoB100</b> <b>LDICRLVAEPEPGSESS-ME-QVLF-PKPGPEPTQRLLSQLERGILVASN KEQRLFLPFSYKKNKYGMVVAQVTQLRKL--EDTPKINSRFFGEGTKKMG</b> <b><u>L*</u> <u>S</u> <u>A</u> <u>P</u></b> <b><u>K</u> <u>M</u> <u>QV</u></b> <b><u>T</u> <u>E</u> <u>*K*</u> <u>S</u> <u>*</u> <u>*</u></b>	<b>ISGF3<math>\gamma</math></b> <b>apoB100</b> <b>PRGLFVQ--RLCPPIPISWNAPQAPPGPGRPHILLPSNECVELFRAYFCR --LAFAESTRKSTSPPKQAEAVLKT<u>L</u>QELKRLTISEQNIQ--RANLFNR</b> <b><u>L</u> <u>*</u> <u>A</u> <u>*</u> <u>*</u></b> <b><u>F</u> <u>*</u> <u>S</u> <u>*</u> <u>*</u></b>	<b>ISGF3<math>\gamma</math></b> <b>apoB100</b> <b>DLVRYFQQLGPPPKFQVTLNFWEESHGSSHTPQNLITVKMEQAFARYL -LVTELRGLSDEAVTSSLPPQLIEVSSPIT-LQALVQCGQPQCSTHL</b> <b><u>V</u> <u>*</u> <u>G</u> <u>L</u></b> <b><u>*</u> <u>*</u> <u>E</u> <u>S</u> <u>*</u></b>	<b>ISGF3<math>\gamma</math></b> <b>apoB100</b> <b>KMEQAFARYLLEQ-TPEQQAAAILSLV RRVHANP-LLIDVVTY---LVALIPE</b> <b><u>K</u> <u>A</u> <u>*</u> <u>L</u> <u>*</u></b> <b><u>*</u> <u>*</u> <u>*</u> <u>L</u> <u>*</u></b>
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\* indicates conserved amino acids  
**bold** type indicates positively charged, basic amino acids

FIG. 8B

Sequence Comparison of DNA-Binding Protein ISGF3 $\gamma$  SEQ ID NO:81; and a Similar Region of Apo B-100 Located Between Residues 2930 and 3324, SED ID NO:83.

MA-SGRARCTRKLRNWVVEQVESQGFPGVWCDD-----	ISGF3 $\gamma$ apoB100
FGLSNKIN-SKHLRVNQNLVYESGSSLNFSKLEIQSQVDSQHVGHSVLR ** S ** LR * ESG *	
TAKTM----FRIPW--KHAGKQDFRESQDAAFFKAWAIFKGKYKEG TARGMALFGEGRKAEFTGRHDARLNGKVIG-TL--RNSLFFSAQPFEI TAK M ** R ** * R ** * R ** F	ISGF3 $\gamma$ apoB100
--DKEVPE-RGRMDVAEPPYKVYQLLPPGIVSGQPGTOKVPSKROHS TASTNEGNLKVRFPLRLTGKI-DFLNNYALFLSPSAQQA-SWQVSA * R * R * R * R * R * L * * L * * L * * L * * L * * L	ISGF3 $\gamma$ apoB100
KRQHSSVSSE---RKEEDAMQNCTLSPSVLQDSLNNNEGASGGAVHS RFNQYKYNQNFSAAGNNENIMEAHVGINEANLDFLNI-PLTIPEMR- * R * R * R * R * R * R * R * R * R * R * R * R * R * R	ISGF3 $\gamma$ apoB100
DIGSSSSSSPEPQEVTOTTEAPFGDQRSLEFLLPPEPDYSLLT -LPYTIITTPPLKDFSLWEKTGLKEFL-RTTKQSFDLSVKAQYKKNK * R * R * R * R * R * R * R * R * R * R * R * R * R * R	ISGF3 $\gamma$ apoB100

FIG. 8C

23/56

Sequence Comparison of DNA-Binding Protein ISGF3 $\gamma$  SEQ ID NO:81, and a Similar Region of Apo B-100 Located Between Residues 2930 and 3324. SED ID NO:83.

**IYNGRVVGEAQVQSLDCRLVAE**PSGSESSMEQVLFPKPGPEPTQRLL  
**HRHSTNPLAVLCEFISQSIKS**FDRHFEKRNNAALDFVTKSYNETRIK  
E—\*\*\*\*\*

**SQLERGILVASN-PRGLFVORLCPIPI**SWNAPOAPPGPGPFLLPSEN  
**FDKYRAEKSHDELPRT-FQIPGYTPV-VNVEVSPFTIEMSAFGYVF**  
\*—\*—\*PRF\/\*\*N\*p\*/\*\*\*

**CVELFRAYF---CRDLVRVYFQQLG**PPPKFQVTLNFMEESHGSSHTP  
**-PKAVSMPFSILGSD-VRVPSYTLILPSLELPVLHVPRNCKLSTPH**  
\*—\*\*FDV\R\*\*\*p\*\*\*\*—\*S

**-QNLITVKMEOFAFARYLLEQTPEQQAAILSLV**  
**FKEELCTISHIFIPAGNITYDFSFKSSVITLN**  
FLT\*—\*A\*—\*\*\*\*L

**ISGF3 $\gamma$**   
**apoB100**  
—\*—\*  
bold type indicates positively charged, basic amino acids  
ISGF3 $\gamma$  = sequence ID No:81. Apo B-100 amino acids (aa  
2930-3324) = sequence ID NO:83.

FIG. 8D

24/56

Various regions of apoB-100 having similarity of ISGF3γ (1-51)

SEQ ID NO:	
MASGRARCTRKLRLNNWVEQVESGQFPVCWDDTAKTMFRIPWKHAGKQDFR	ISGF3γ(1-51)
-PKDATRFKHLRKYTNYEAESSSGVPGTAD-SRSATRINCKVELEVILPQ	apoB(13-59)
-PEGKALLKKTKNSEEEFAAM-----SRYELKLAIP-EGKVFL	apoB(80-116)
-CSTHFTVKTRGNVATEIST-----ERDLGQCDFKPIRTGIS	apoB(159-196)
CSTHILQWLKRVHANPLLIDWVTLVALIPEPSAQQLREIFNMARDQRSRA	apoB(363-413)
HLSCDTKEERKIKGVISI-----PRLQEARSEILAHWSPAKL	apoB(1082-1119)
-SVHLDSSKKKQHLFYKEVKIDGQFRVSSFY-AKGTYGLSCQRDPNTGRL	apoB(1441-1487)
KHINIDQFVRKYRAALGKLQQANDYLNFNWERQVSHAKE-----	apoB(2073-2113)
-KLTALEKKYRITENDIQIA-----LDDAKINFNEKLSQLQTYMIQ	apoB(2114-2153)
-ERINDVLEHVVKHFVINLIGDFEVAEKINAFAKVHELIERYEVDQOIQVL	apoB(2281-2330)
-NKFLDMLIKKLKSFDYHQFVDETNDKIREVTQRLNGEIQAELPQKAEAL	apoB(2390-2439)
-SNKINSKHLRVNQNLVYESGSLN-----	apoB(2933-2955)
-FSKLEIQSQVDSQHVGHSVLTAKGMALFGE GGKAETFTGRHD AHLNGK	apoB(2956-3001)

FIG. 9A

25/56

## Various regions of apoB-100 having similarity of ISGF3γ (1-51)

<u>KLDVTTSIGRRQHLRVSTAFVYTKNPNGYSFSIPVKVLAD<u>K</u>ITPGL<u>K</u>LND</u>	APOB(3662-3712)	99
-- <u>FREIQIYKKLRTSSFA<u>N</u>LP<u>T</u>LP<u>E</u>V<u>K</u>PEVDVL<u>T</u>KYSQPED<u>S</u>LI<u>P</u>FFF<u>I</u></u>	APOB(3738-3786)	100
-- <u>LHLRYQ<u>KDKKG</u>I<u>STSAASPAVGTVGMDMDEDDDFSKWNFYSPQSSPD</u></u>	APOB(3959-4006)	101
-- <u>LREVSS<u>KLRRNLQNNAEWVYQGAIRQIDDIDVRFQKAASGTTGT<u>YQEW</u></u></u>	APOB(4070-4117)	102
-- <u>RVTQK<u>FHMKV<u>KHL</u>IDSLIDFLNFP<u>R</u>FQPG<u>KPGI</u>YTREELCTMFIREVGT</u></u>	APOB(4150-4199)	103

FIG. 9B

26/56

Various regions of apoB-100 having similarity of ISGF3 $\gamma$  (42-69)

SEQ ID NO:

WK <u>HAGKQDFRESQDAFF</u> -----KAWAIF <u>GKYYKEG</u> -D <u>KEVPERGRMDVAEPYK</u>	iSGF3 $\gamma$ (42-69)	104
E <u>HVKH</u> FVINLIGD-----FVAE <u>KINA-FRAKVHELIERYEVDQQIQVLMDKL</u> V	APOB(2288-2335)	105
<u>VRKYRAALGKL</u> PQQANDYLNSFNWERQS-----H <u>AKEKL</u> TAL <u>TKYKRITENDIQIA</u>	APOB(2081-2132)	106
<u>YIKDSYDLHDL</u> KIAIANIIDEIEKL <u>KSLSDEHYHIRVNVLVKT</u> I <u>HDL</u> H <u>LFIFIENIDFNK</u>	APOB(2157-2213)	107
-----K <u>ITLIIINWLQEALSSASLAHMKAKFRETLEDT</u> R-----	APOB(2461-2493)	108
-----T <u>DHFSLRARYIMKADSVVDSL</u> SYNQGSGETTY	APOB(1353-1385)	109
-----K <u>LTTNGRFREHNNAKFSIDGK</u> -----	APOB(1656-1675)	110
<u>DTKYQIRIQI</u> QE <u>KLQLKRHI</u> QNIDIQ <u>HLAGKL</u> K <u>QHIEAIDV</u> R <u>VLLDQLGTT</u> -----	APOB(2226-2277)	111
-----F <u>HDFPDLGQEVALNANTKNQK</u> 1 <u>RWKNEVR</u> I <u>HSGSFQSQVELSNDQ</u> -----	APOB(3583-3627)	112
-----K <u>DNVF</u> DGL <u>V</u> R <u>VTQKFHMKV</u> KHL <u>IDSLIDFLNFPR</u> -----	APOB(4141-4174)	113
-----H <u>RNIQEVLSIL</u> T <u>DPDGKGEK</u> I <u>AELSATAQEIJKS</u> -----	APOB(4418-4452)	114

FIG. 9C

Sequence Comparison of DNA-Binding Domains of SREBP 1 (aa 279-452) SEQ ID NO:116, SREBP 2 (aa 287-568) SEQ ID NO:117 and ADD1 (aa 250-421) SEQ ID NO:118 to a Similar Region of Apo B-100 (aa 2024-2234) SEQ ID NO:115.

EFTIVAFVKYDKNQDVHSINLPFFETLQEYFERNRQTIIIVVLENQ	AP0B100
GPLPTLVSGGTILATVPLVVDAAEKLPIINRLAAGSKAPASAQS <sub>R</sub> -GE	SREBP1
QVPTLVGSSGTILTTPMPVMQEQKVPIKQVPGGVQ-LEPPKE-GE	SREBP2
GPLQTLVSGGTILATVPLVVDTDKLPPIHRLAAGGKALGSAQS <sub>R</sub> -GE	ADD1
***** V * * * * Q * * * E * *	
RKLKHINIDQFVRKYRAAL -GKL PQQANDYLNSFNW <sub>R</sub> ERQVSHAKEK	AP0B100
KRTAH-NAIE- -KRYRSSINDK <sub>I</sub> IELK- -DL VVGTEAKLNKS <sub>R</sub> AVLRK	SREBP1
RRTTT <sub>H</sub> -NIE- -KRYRSSINDK <sub>I</sub> IELK- -DL VMG TDAKM <sub>H</sub> KSGVLRK	SREBP2
KRTAH-NAIE- -KRYRSSINDK <sub>I</sub> VELK- -DL VVGTEAKLNKS <sub>R</sub> AVLRK	ADD1
R* H N I * * * YR*** K*** D** * * * S * K	
L T A L T K Y R I T E N D - I Q I A L D D A K I N F N E K L S - - - - - Q L Q T Y M I Q F	AP0B100
A I D Y I R - F L Q H S N Q K L K Q E N L S R T A V - H K S K S L K - - D L V S A C - - -	SREBP1
A I D Y I K - Y L Q Q V N H K L R Q E N M V L K L A - N Q K N K L L K G I D L G S L V - - -	SREBP2
A I D Y I R - F L Q H S N Q K L K Q E N L T L R S A - H K S K S L K - - D L V S A C - - -	ADD1
* * K Y N * * * K * * N * K * L ***	

28/56

Sequence Comparison of DNA-Binding Domains of SREBP 1 (aa 279-452) SEQ ID NO:116, SREBP 2 (aa 287-568) SEQ ID NO:117 and ADD1 (aa 250-421) SEQ ID NO:118 to a Similar Region of Apo B-100 (aa 2024-2234) SEQ ID NO:115.

GPLPTLVSGGTILATVPLVVDAE <u>K</u> LPI <u>N</u> RLAAGSKAPASAQSR <u>G</u> E	AP0B100
QVPTLVGSSGTILTTMPVMMGQE <u>K</u> VPKQVPGGVK <u>G</u> -LEPPKE <u>G</u> E	SREBP1
GPLQTLVSGGTILATVPLVVDTDKLPI <u>H</u> RLAAG <u>K</u> ALGSAQSR <u>G</u> E	SREBP2
***** V * * * * Q * ** E *	ADD1
RKLKHINIDQFVRKYRAAL - GKL <u>P</u> QQANDYLNSFNW <u>R</u> EV <u>S</u> HAKE <u>K</u>	AP0B100
KRTAH-NAIE--KRYRSSIND <u>K</u> I <u>E</u> L <u>K</u> -DLVVGTEAKLN <u>K</u> SAVL <u>R</u> K	SREBP1
RRTT <u>H</u> -N1IE--KRYRSSIND <u>K</u> I <u>E</u> L <u>K</u> -DLV <u>M</u> GTD <u>A</u> KM <u>H</u> KSGV <u>L</u> R <u>K</u>	SREBP2
KRTAH-NAIE--KRYRSSIND <u>K</u> I <u>E</u> L <u>K</u> -DLVVGTEAKLN <u>K</u> SAVL <u>R</u> K	ADD1
R* H N1 * *YR*** K*** D** * * * S * K	
LITALTKKYRITND-IQIALDDAKIN <u>N</u> FE <u>K</u> L <u>S</u> -----QLQTYMIQF	AP0B100
AIDYIR-FLQHSN <u>K</u> L <u>Q</u> EN <u>L</u> SLRTAV-HKS <u>K</u> SL <u>K</u> --DLV <u>S</u> AC---	SREBP1
AIDYIK-YLQQVN <u>H</u> <u>K</u> L <u>Q</u> EN <u>M</u> <u>V</u> <u>L</u> <u>K</u> LA-N <u>Q</u> <u>K</u> <u>N</u> <u>K</u> <u>L</u> <u>G</u> <u>D</u> <u>G</u> <u>S</u> <u>L</u> ---	SREBP2
* * K Y N* * *K* *N*K *L ***	ADD1

Sequence Comparison of SREBP1 to Apolipoprotein apo A1  
apoA1 (1-243) SEQ ID NO: 119 and SREBP1 (aa 233-500) SEQ ID NO:120

DEPPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQLGPVTQEFWDN QQVPVLLQPFITKA <u>D</u> SSLTTAM <u>K</u> TDG <u>A</u> TVK - - - AAGLSPLVSGTTVQTG - PLPTLVSGG - - TILATVPLVVD- ***p * <u>X</u> * * <u>X</u> * *** * <u>X</u> R\ / G * **L *X**S *X*	apoA1 SREBP
LEKEETEGLRQEMSKDLEEVKAKVQPYLDDFQKKWQEEMELYRKVEPLRAELQEGARQKLH <u>E</u> L SPLGEE AEKLPINR <u>A</u> AGSKAPASA <u>S</u> RG - - - - E <u>R</u> RTAHNAIEKRY <u>R</u> SS <u>I</u> N <u>D</u> KI <u>I</u> E <u>L</u> K <u>D</u> V <u>V</u> GTEAKLN <u>K</u> SAVL - - - *ER <u>T</u> / SR * * <u>X</u> * * <u>X</u> R * <u>X</u> / <u>R</u> * <u>X</u> *X**L *X*	apoA1 SREBP
MRDAR - - AHVDALRTHLAPYSDELRQR <u>L</u> AARLEA - LKEN - - - - GGARLA <u>E</u> Y - HAKATE - - - - - - <u>R</u> -K <u>A</u> T <u>D</u> Y <u>I</u> RF - L <u>Q</u> <u>F</u> S <u>N</u> Q <u>Q</u> KL <u>K</u> Q <u>E</u> N <u>L</u> <u>S</u> <u>L</u> <u>R</u> <u>T</u> <u>A</u> <u>R</u> <u>K</u> <u>S</u> <u>K</u> <u>L</u> <u>V</u> <u>S</u> <u>A</u> <u>C</u> <u>G</u> <u>S</u> <u>G</u> <u>N</u> <u>T</u> <u>D</u> <u>V</u> <u>L</u> <u>M</u> <u>E</u> <u>G</u> <u>V</u> <u>R</u> - TEVEDTLTPPPSDAG R * <u>X</u>	apoA1 SREBP
SPFQSSPLSLGSRGSGSGSGSDSEPDSPVF - - - - ED <u>S</u> <u>K</u> <u>A</u> <u>P</u> - - EQ - R <u>P</u> <u>S</u> <u>L</u> <u>H</u> <u>S</u> <u>R</u> <u>G</u> <u>M</u> <u>L</u> <u>D</u> <u>R</u> - SRL - AL <u>C</u> <u>T</u> <u>L</u> <u>V</u> <u>F</u> <u>L</u> <u>C</u> - - LNTQ LSCN L *	apoA1 SREBP

FIG. 10C

30/56

Sequence Comparison of apoAII (1-77) SEQ ID NO:121 and SREBP1 (aa 353-423)  
 SEQ ID NO:122

QAKEPCVESLVSQYFQTVTDYGKDLM--	-EKVKSP <del>E</del> LQAEAKSYFEKSKEQLTPLIKKAGTELVNFLSYFVEL-	apoA-II
<del>EAKLNK</del> --SAVLRKA <u>I</u> --	-D <del>Y</del> IRFLQHSNQKL <u>R</u> QENL <u>S</u> L--RTAV <u>H</u> R <u>S</u> K <u>S</u> -LK <u>D</u> L <u>V</u> <del>S</del> <u>A</u> C <u>G</u> <u>S</u> <u>G</u> -GNTD-VLMEGV-	SREBP1
* <u>R</u> \ /	D <del>Y</del> * <u>L</u> * <u>R</u> * <u>K</u> * <u>L</u> * <u>R</u> * <u>K</u> * <u>T</u> SK	
	L _ L * G* N **E	
		apoA-II
		SREBP1

GTQPATQ  
 KTEVEDT  
 -T\*\* \ /

31/56

Sequence Comparison of apoAIV (30-376) SEQ ID NO:123 and SREBP1 (aa 330-1146) SEQ NO:124

QKSELTOQLNALFQDKLGEVNTYAGDLQKKLVPFATELHERLAKEEIGKELE---ELRA-R-LLPH *R * *L A R* G* K* * A E R * * R* E * R*L	apoAIV SREBP1
-ANEVSQKIGDNLRELQRRLTEPYADQLRTQVNITQAEEQLRRQLDPLAQ--RMERVRENADS-LQASLRPH-- KAIDY-IRFLQHS---NQKLQENLSLRTAVHKSKS-LK-DLVACGSGGNTDVLMEGVKTEVEDTLTPPPR -A ** * Q* L R T V _ L * L *	apoAIV SREBP1
DAGSPFQSSPLSLGSRGSGSGSDSEPDSPVFEQRP-SLHSR---GMLDRSRLALCTLVFLC [SCNPLASLLGARGLPSPSDTTSVYHSPGRNVLTGESRDGPWAQAVQLFTCDLLLVRRTSLWRRQQ-TQPPAP S P*A * T * Q*V* * S * Q*V* * L*** * * Q*V* **	apoAIV SREBP1
TFQMKKNAEELKARISSAAELKARISSAAEELR--QR---LAPLAEDVRGNLKGNNT--EGLOKSLSAELGGHL DQQVVEE--F APAAGASSRP---QASALEIRGFQRDLSSLRRAQSFRPAMRRVFLHEATARLMAGASPTTRTHQLLDRSL ** * * R ASA ELR QR L LA* *R * R * A *	apoAIV SREBP1
RRRVEPYGENFNKALVQOMEQLRQKLGPHAGDVEGHLS-FLEKD----LRDKVNFFFSTFKEKESQ-DKTLS RRRAGPGGGKG--AVAE-LE-PRPTREHA-EALLLASCYLPPGFLSAPGQRVGMLAEAARTTEKLGDRLR- RRR* P G * *** * E * R RA * * S * L * * V * * E D* L	apoAIV SREBP1

FIG. 10E

Sequence Comparison of apoAIV (30-376) SEQ ID NO:123 and SREBP1 (aa 330-1146  
 SEQ ID NO:124

```
LPELEQQEQQQEQVQMLAPLES
LHDCQ-----MLMRGGGTTVTSS
** Q S
```

FIG. 10F

Sequence Comparison of acat (fragment 1) SEQ ID NO:125 and SREBP1  
 (aa 300-486) SEQ ID NO:126

```
EKMSLRNRLS-KSRNPEEDED-QRNPAKESLETPSNGRIDIKQLIA
ER* * NR* SF * * AF***E
```

```
KKIKL TANGRI-DIKQL IAKK-IKL TAENGRIDIQLIAKKIKLTAE
KRYRSSINDRIIEKLDLWGTAEKLNKSYTIRFLQS-NQRLQENL
KF**N I **R*L ** *RL R*V/F R*K
```

```
AEELKPFFMKEVGSHFDDFVT-----NLI-EKSAS-LDNKAHSF
S--LRTAVHRSKSLR--DLVSACGGGGNTDVLMEGVKTVEVEDKRPE
* LF**R D*V* D*V* E * ***RAF
```

```
VRENV-PR-VLNSAKEK
QRPSLHSRGMLD-RSR
```

FIG. 10G

33/56

Sequence Comparison of acat (fragment 2) SEQ ID NO:127 with  
SREBP1 (aa 1061-1085) SEQ ID NO:128

```

RRHC-PLKNPTFLDYVRPRSIWTCRYVF
RRRAGPGGKGGAAELEPRPTRREH_
RRR* P ** * PR

```

**FIG. 10H**

Sequence Comparison of apoE (aa 124-181) SEQ ID NO:129 and SREBP1 (aa 302-360) SEQ ID NO:130

```

AMLGQSTEE-LRVRLA--SHL-RKLRKRLRADDLQKRL-AVYQAGAREGAERGLSAIRE-RL
KLPIINRLAAGSKAPASAQSRSRGEKRT---AHNA--IEKRYRSSIN--DKIIELKDLVVGTEAKL
** * ** S* ** S* ** *** ** KR* * ** * ** ** ** ** ** ** **

```

```

apoE
SREBP1

```

```

--GPLVEQGRVRAATVGSLAGQPLQERAQAWGERLRARMEEMGSRT-RDRLDEVKEQVA
NKSAVL---R-KAIDYIRFLQHSNQKTQENLSLRTAVHK--SKSLRDLVSAGSGG
*** R RA* * ** Q Q LR* LR* SK* SK* RD D 1 * *D 1 *

```

**FIG. 10I**

Sequence Comparison of apoC-II (aa 1-42) SEQ ID NO:131 with SREBP1 (aa 231-275) SEQ ID NO:132

TQQPQQDEMPSPTFLTQVK-----ES----LSSYWE---	SAK TAAQNLYEKTYL
SQ-IQQ-----VPVLLQPHFIKADSLLLTAMKTDGATVK <del>A</del> GLSPLVSGTT	apoC-II SREBP1
*Q *QQ ----- *L Q*** A *S L***	**R*A* **

FIG. 10J

Sequence Comparison of apoC-II (aa 7-51) SEQ ID NO:133 with SREBP1 (aa 314-360) SEQ ID NO:134

SLLSFMQGYMKHATKTAKDAL--SSVQESQVAQQARGWVTDGFSSLK--	apoC-II SREBP1
APASAQS <del>R</del> GERRTAHNATEKRYRSSIND-KIIE-L <del>K</del> DLVVGTEAKLNKS	
*SS*** A * <u><u>S</u></u> K***	** R ***

FIG. 10K

35/56

Sequence Comparison of APO C-III (aa 52-79) SEQ ID NO:135 with  
SREBP1 (aa 717-748) SEQ ID NO:136

DYWST - VKDKFSEFWLDPEVRP -- TSAVAA	apoC-III
EIYVAAALRVRTSLPRALHFLTRFFLSSARQA	SREBP1
*** * * K S * L * R * * SA A	

FIG. 10L

Sequence Comparison of apo D (aa 30-34) SEQ ID NO:137 with SREBP1  
(aa 301-305) SEQ ID NO:138

EKIPT	apoD
ERLPI	SREBP1
ER*P	

FIG. 10M

36/56

Sequence Comparison of apo D (aa 36-65) SEQ ID NO:139 with SREBP1  
(aa 361-391) SEQ ID NO:140

ENGR**C**IQANYS-LME-NGKIKVLNQELRADG  
AVL**R**KA-IDYIRFLQHSNQK[KQENLSERTAV

**FIG. 10N**

Comparison of the Primary Structures of Known Coiled-Coil Regions of  
DNA-Binding Proteins and Analogous Regions in Apo B-100

MKQL <del>E</del> DKV <del>E</del> LLSKNYH <del>L</del> ENEVAR <del>L</del> KKLVGER	GCN4-p1	(SEQ ID NO: 141)
KHE <del>I</del> <del>I</del> QEMFDQLR <del>A</del> KEKELRTWEEEL <del>L</del> TRAALQQ	hMLK1(286-317)	(SEQ ID NO: 142)
EELL <del>R</del> RREQELAEREIDILERELN <del>I</del> I <del>H</del> QLCQ	hMLK1(321-352)	(SEQ ID NO: 143)
RIQI <del>Q</del> EKLQOLKRHIQNI <del>D</del> I <del>O</del> HLAGKLQHIE	apoB(2232-2264)	(SEQ ID NO: 144)
VLQQVKIKDYFEKLVGFI <del>D</del> DAVKKL <del>N</del> ELSFKTFIE	apoB(2353-2387)	(SEQ ID NO: 145)
ELSFKTFIEDVNKF <del>L</del> DMLIKKLKS <del>F</del> DYHQFV	apoB(2379-2409)	(SEQ ID NO: 146)
HQFVDETN <del>D</del> K <del>I</del> REV <del>T</del> QRLNGEIQ <del>A</del> LELP	apoB(2406-2433)	(SEQ ID NO: 147)
AAKN <del>L</del> TDFAEQYSIQDWA <del>K</del> RMKA <del>L</del> VEQGFTV	apoB(2530-2560)	(SEQ ID NO: 148)
SASLAHMKA <del>K</del> AKFRET <del>L</del> EDTRDRM <del>Y</del> DMDI <del>Q</del> QELQRYL	apoB(2475-2509)	(SEQ ID NO: 149)
CLNLHKFNEF <del>I</del> QNELQEASQELQQIHQYIMALREE	apoB(4326-4360)	(SEQ ID NO: 150)
FLIY <del>I</del> TELLKKLQS <del>T</del> VMNPYMKL <del>A</del> PGE <del>L</del> T <del>I</del> L	apoB(4504-4536)	(SEQ ID NO: 151)

FIG. 11

Comparison of Known ATP-Binding loop Motifs to Similar Regions in Apo B-100. The critical amino acid H is indicated by (#)

**A: THE HIGH LOOP**

RLLDHRVPETDMTFRHVGSKLIVAMSSWLQ	apOB(1183-1212) (SEQ ID NO:152)
LNFSKLEIQSQVDSQHVGHSQLTAKGMALF	apOB(2954-2983) (SEQ ID NO:153)
NQNFSAGNNENIMEAHVGINGEANLDLNLN	apOB(3072-3101) (SEQ ID NO:154)
MVVTRIAPSPT-GDPHVGTAYIAFLNYAWA	TTETS(1-29) (SEQ ID NO:155)
TTVHTRFPPEPNNGYLHIGHAKSICLNFGIA	ECQTS(25-54) (SEQ ID NO:156)
KIKLYCGVDPTAQSLHLGNLVPMVLLHFYV	YSCMSY1(85-114) (SEQ ID NO:157)
PIALYCGFDPTADSLHLGHLVPLLCLKRGQ	ECOTYRS(33-62) (SEQ ID NO:158)
RVTLYCGFDPTADSLHIGNLAAITLRRFQ	BACTYRSA(30-59) (SEQ ID NO:159)
RIGAYVGIDPTAPSLHVGHLLPLMPLFWMY	NEUTYRSM(95-124) (SEQ ID NO:160)
PIALYCGFDPTADSLHLGHLVPLLCLKRFQ	SYY ECOL I(31-61) (SEQ ID NO:161)
PLKVKLGADPTAPDIHLGHTVVLNKLRQFQ	HEAHII1610(31-60) (SEQ ID NO:162)

#

**FIG. 12A**

Comparison of Known ATP-Binding loop Motifs to Similar Regions in Apo B-100. The critical amino acid K is indicated by (#)

B: THE KMSK LOOP								
VSKGLLIFDASSSMGPQMSASVHLDSSKKQHLFVKEVKIDGQF	apoB(1421-1463)	(SEQ ID NO. 163						
TIIITPPPLKDFSLWEKTGLKEFLKTTKQSFDSLKVKAQYKKNNKH	apoB(3113-3155)	(SEQ ID NO. 164						
KNRNNNALDFVTKSNETK----IKFDKYKAESQDELPRTFQI	apoB(3183-3221)	(SEQ ID NO. 165						
DALQYKLEGTTRL---TR----KRGLKLATALSLSNKFVEGSH	apoB(3348-3390)	(SEQ ID NO. 166						
RAFGWEAPREYHMPLLNPDK-TKISKRKSHTSLDWYKAEGFL	tttets(221-262)	(SEQ ID NO. 167						
DNITIPVHPRQYEFSRLNLEY-TVMSKRKLNLVTDKHVEGMD	ecqts(245-287)	(SEQ ID NO. 168						
KNKGK--PFGITVPLLTATGE-KFGKSAGNAVFIDPSINTAY	YSCMSY1(282-320)	(SEQ ID NO.169)						
RLHQHQ-VFGLTVPPLITKADG-TKFGKTEGGAVWDPKKTSPY	ECOTYRS(215-254)	(SEQ ID NO. 170						
KTKGEARAFGLTIPLVTKADG-TKFGKTESGTIWLDKEKTSFY	BACTYRSA(210-249)	(SEQ ID NO. 171						
KTALDE-CVGFTVPLLTDSGG-AKFGKSAGNAIWLDPYQTWSVF	NEUTYRSM(303-343)	(SEQ ID NO. 172						
RLHQHQ-VFGLTVPPLITKADG-TKFGKTEGGAVWDPKKTSPY	SYY ECOLI(213-253)	(SEQ ID NO. 173						
SAGKK-PQVAITLPLLVLGLDGEKKMSKSLGNYIGVTEAPSDMF	HEAHI1610(202-243)	(SEQ ID NO. 174						

#

Comparison of Known ATP-Binding loop Motifs to Similar Regions in Apo B-100. The critical amino acid K is indicated by (#)

**B: THE KMSK LOOP**

VSKGLLIFDASSSMGPQMSAVHLDSSKKQHLFVKEVKIDGQF	apoB(1421-1463)	(SEQ ID NO. 163)
TITTPPLKDFSLWEKTGLKEFLKTTKQSFDLSVKAQYKKNKH	apoB(3113-3155)	(SEQ ID NO. 164)
KNRNNALDFVTKSYNETK----IKFDKYKAEKSQDEL PRTFQI	apoB(3183-3221)	(SEQ ID NO. 165)
DALQYKLEGTRL---TR-----KRGCHKLATASLSNKFVEGSH	apoB(3348-3390)	(SEQ ID NO. 166)
RAFGWEAPREYHMPLLRLNPDK-TKISKRKSHTSLDWYKAEGFL	tttets(221-262)	(SEQ ID NO. 167)
DNITIPVHPRQEFSRLNLEY-TVMSKRKLNLLVTDKHVEGWD	ecqts(245-287)	(SEQ ID NO. 168)
KNKGGL--PFGITVPLLTTTATGE-KFGKSAGNAVFIDPSINTAY	YSCMSY1(282-320)	(SEQ ID NO. 169)
RLHQNQ-VFGITVPLITKADG-TKFGKTEGGAWLDPKKTSFY	ECOTYRS(215-254)	(SEQ ID NO. 170)
KTKGEARAFGLTIPLVTKADG-TKFGKTESGTIWLDKEKTSFY	BACTYRSA(210-249)	(SEQ ID NO. 171)
KTALDE-CVGFTVPLLTDSSG-AKFGKSAGNAIWLDPYQTSVF	NEUTYRSM(303-343)	(SEQ ID NO. 172)
RLHQNQ-VFGITVPLITKADG-TKFGKTEGGAWLDPKKTSFY	SYY ECOLI(213-253)	(SEQ ID NO. 173)
SAGKK-PQVAITLPLLVGLDGEKKMSKSLGNYIGVTEAPSDMF	HEAHI1610(202-243)	(SEQ ID NO. 174)

#

**FIG. 12C**

Examples of Nuclear Localization Signal Sequences in the ApoB-100 Amino Acid Sequence Compared to Known NLS Sequences.

Human apoB-100 sequences with 10 amino acids in the spacer region between the bipartite NLS element

SEQ ID NO.	Sequence	Source of Sequence
178	HKNTSTLSCDGSLRHKF	human apoB-100 (1387-1403)
179	RKLKHINIDQFVRKYRA	human apoB-100 (2070-2086)
180	RHIQNIIDIQHLAGKLQH	human apoB-100 (2244-2261)
181	KKGFYKKKQCRPSKGK	human IGFBP-3
182	KKPLDGEYFTLQIRGRER	human p53 fragment 1
183	KRALPNNTSSSPQPKKK	human p53 fragment 2
184	KKTNLFSAIJKLMNOP	human Ab1
185	RKTLLNSLEAKKKED	human apoJ fragment 1
186	RRELDLQVAERLTRK	human apoJ fragment 2

FIG. 13A

Human apoB-100 sequences with 10 amino acids in the spacer region  
between the bipartite NLS element

SEQ ID NO.	Sequence	Source of Sequence
187	RRSYALVSLSSFFRKRLR	human irf fragment 1
188	RRYGDEELHLCVSRKHF	human irf fragment 2
189	KRVAKRKLIEQNRERRR	human thyroid receptor fragment 1
190	HRSTNAQGSHWKQRRKF	human thyroid receptor fragment 2
191	KRPPISDSEELSAAKKRK	human afg
192	KKGKKPKTEKEDKVVKHI	human irf2
193	RKRMRRNRIAASKCRKRK	human apl

IGFBP-3 = interferon growth factor binding protein 3; apoJ = apolipoprotein J; ir- insulin receptor; afg-activation factor 9; irf-insulin response factor 2; apl = activation protein 1

FIG. 13B

43/56

Human apoB-100 sequences with more or less than 10 amino acids  
in the spacer region between the bipartite NLS element

SEQ ID NO.	Sequence	Source of Sequence
194	RHIQNIDIQHLAGKLKQH	human apoB-100 (2244-2261)
195	KKITEVALMGHLSCDTKEERK	human apoB-100 (1072-1094)
196	KHINIDQFVRKYRA	human apoB-100 (2073-2086)
197	HRNIQEYLSILTDPGKGKEK	human apoB-100 (4418-4438)

FIG. 13C

44/56

Human apoB-100 sequences with more or less than 10 amino acids in the spacer region between an imperfect bipartite NLS element

SEQ ID NO.	Sequence	Source of Sequence
198	KEVYGFNPEGKALLKKTK	human AP0B100 73-90
199	KVLVDHFGYTKDDKHEDM	human AP0B100 705-723
200	KAGKLKFIIIPSPKRPVKL	human AP0B100 891-908
201	RQVSHAKEKLTAALKYR	human AP0B100 2106-2123
202	KYQIRIQIQEKLQQQLKRH	human AP0B100 2228-2245
203	KGMALFGEGKAETFGRHDH	human AP0B100 2978-2997
204	KQSFDLSVKQAQYKKNNKHR	human AP0B100 3139-3156
205	KLEGTTTRLTRKGGLK	human AP0B100 3353-3367
206	KLDVTTSIGRRQHLR	human AP0B100 3662-3676
207	KLDFREIQIYKKLR	human AP0B100 3735-3748

FIG. 13D

45/56

Human apoB-100 sequences with more or less than 10 amino acids in the spacer region between an imperfect bipartite NLS element

SEQ ID NO.	Sequence	Source of Sequence
208	KSPATDLHLRYQKDKK	human AP0B100 3952-3968
209	KYHWEHTGTLREVSSKLRR	human AP0B100 4060-4079
210	KDNVFDGLVRVTQKFHMVKKH	human AP0B100 4141-4161

FIG. 13E

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SE ID NO:216 apoB-100 Sequences

LNDFQVPDLH <del>I</del> PEFQLPHI <del>S</del> H <del>T</del> IEVPTFGK <del>L</del> YSILKIQSPLFTLDANADIGNGTTSANE-	Human (2701-2760)
EFQLPR <del>I</del> SHTIEIPAFGR <del>L</del> HGILKIQSPLFILDANANIONVTTLENKAE	Hamster ( frag 1)
EFQLPHL <del>S</del> H <del>T</del> IEIPAFGK <del>L</del> H <del>S</del> ILKIQSPLFILDANANIQNVTTSGNKAE	Mouse ( frag 1)
GIAASITAKGESKLEVLNFDFQANAQLSNPKINPLALKESVKFSSKYLRTEHGSEMLFFG	Human (2761-2820)
IVASIAAT-GESE <del>E</del> IEALNFDFQAAQAFLELNPNPLILKESMNFSSKKHARMEHEGEIELFSG	Hamster ( frag 1)
IVAS-VTA <del>K</del> GESQFEALNFDFQAAQAFLELNPHPPV <del>L</del> KESMNFSSKKHVRMEHEGEIVFDG	Mouse ( frag 1)
NAIEGKSNTVASL <del>H</del> TEKN <del>T</del> ELNSNGVIVKINNQLTLDSNTKYFHKLNIPKLDFSSQADLR	Human (2821-2880)
KFIEGK <del>L</del> D <del>T</del> VASL <del>Q</del> TEKNMVEFNNGMIVKINNPIIILDSHTK <del>Y</del> FHKLSIPRLDFSSKASFN	Hamster ( frag 1)
KAIEGK <del>S</del> DTVASL <del>H</del> TEKNEVEFNNGM <del>T</del> V <del>K</del> NNQLTLD <del>S</del> H <del>T</del> K <del>Y</del> FHKLSV <del>P</del> R <del>L</del> DFSSKASLN	Mouse ( frag 1)
NEIK <del>T</del> LLKAGHI <del>A</del> WTSSGKGS <del>M</del> WACPRFSDEGTHEQSISFTIEGPLTSFGLS <del>N</del> KINSKH	Human (2881-2940)
NEIK <del>M</del> LL <del>E</del> AGHVA <del>W</del> ATSSGTGS <del>W</del> WACPNFSD <del>E</del> GTH <del>S</del> SKISFTVEGPIAFFGLS <del>N</del> NINGKH	Hamster ( frag 1)
NEIK <del>T</del> LL <del>E</del> AGHVA <del>L</del> TSSGTGS <del>W</del> WACPNFSD <del>E</del> GIHSSQISFTVDGPIAFVGLS <del>N</del> NINGKH	Mouse ( frag 1)
LRVNQNLVYESGSLNFSKLEIQSQVDSQH <del>G</del> HSVLTAKGMA <del>L</del> F <del>G</del> EGKA <del>E</del> FTGR <del>H</del> DAHLNG	Human (2941-3000)
LRVIQKL <del>A</del> YESGFLNYSM <del>E</del> VES <del>K</del> VE <del>S</del> QHVGSSILTGK <del>G</del> TV <del>L</del> REAKA <del>E</del> MTGEHNADLN <del>G</del>	Hamster ( frag 1)
LRVIQKL <del>T</del> YESGFLNYSK <del>F</del> EV <del>E</del> VE <del>S</del> QHVGSSILTANGRALLKD <del>A</del> EMTGEHNANLN <del>G</del>	Mouse ( frag 1)
KVIGTLKNSLFFSAQPFEITASTNNEG <del>N</del> LKVRFPLRLTGKIDFLNNYALFLSPSAQQASW	Human (3001-3060)
KVIGTLKNSLFFSAQP <del>F</del> MITASTNDGNLKVSFPLKL <del>T</del> GKIDFLNNYALFLSPHAQQASW	Hamster ( frag 1)
KVIGTLKNSLFFSAQPFEITASTNNEG <del>N</del> LKVGFPLKL <del>T</del> GKIDFLNNYALFLSPRAQQASW	Mouse ( frag 1)

**FIG. 14A**

47/56

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SE ID NO:216 apob-100 Sequences		
LNDFQVPDLH <del>I</del> PIEFQLPHISHTIEVPTFGKLYSILKIQSPLFTLDANADIGNGTTSANEA-	Human (2701-2760)	
EFQLP <del>R</del> LSHTIEIPAFGRLHGILKIQSPLFILDANANIONVTTLENKA-	Hamster (frag 1)	
EFQLP <del>H</del> LSHTIEIPAFGKLHSILKIQSPLFILDANANIONVTTSGNKA-	Mouse (frag 1)	
GIAASITAKGE <del>S</del> KEVLNFDFQANAQLSNPKINPLALKESVKFSSKYLRTEHGSEMLFFG	Human (2761-2820)	
IVASIAAT-GESEIEALNFDFQAAQFLELNPNPPLIKESMNFSSKKHARMEHEGEILFSG	Hamster (frag 1)	
IVAS-VTAKGE <del>S</del> QEALNFDFQAAQFLELNP <del>H</del> PPVLPKESMNFSSKKHVRMEHEGEIVFDG	Mouse (frag 1)	
NAIEGKSNTVASLHTEKNTLELSNGVIVKINNNQLTLDNTK <del>Y</del> FHKLNIPKLD <del>F</del> SSQADLR	Human (2821-2880)	
KFIEGKLDTVASLQTEKNMVEFNNGMIVKINNPIIILDSHTK <del>Y</del> FHKLSPR <del>L</del> D <del>F</del> SSKASFN	Hamster (frag 1)	
KAIEGK <del>S</del> DTVASLHTEKNEVEFNNGMTVKVNQNQLTLD <del>S</del> HTK <del>Y</del> FHKLSPV <del>R</del> L <del>D</del> SSKASLN	Mouse (frag 1)	
NEIKTLLKAGHIAWTSSGKG <del>S</del> W <del>K</del> WACPRFSDEGTHESQISFTIEGPLTSFGLSNN <del>N</del> SKH	Human (2881-2940)	
NEIKMLLEAGHVAWTSSGTGSWNWACPNSDEGTHSSKISFTVEGPIAFFGLSNN <del>N</del> INGKH	Hamster (frag 1)	
NEIKTLLEAGHVALTSSGTGSWNWACPNSDEGIHSSQISFTVDGPIAFVGLSNN <del>N</del> INGKH	Mouse (frag 1)	
LRVNQNLVYESGSLNFSKLEIQSQVDSQHVGHSVLTAKGMALFGE <del>G</del> KA <del>E</del> FTGRHD <del>A</del> HLNG	Human (2941-3000)	
LRVIQKLAYESGFLNYSM <del>E</del> VESKVESQHVGSSILTGK <del>G</del> T <del>V</del> LLRE <del>A</del> KA <del>M</del> TGEHNADLN <del>G</del>	Hamster (frag 1)	
LRVIQKLTYESGFLNYSKFEVESKVESQHVGSSILTANGRALLKD <del>A</del> KA <del>M</del> TGEHNANLN <del>G</del>	Mouse (frag 1)	
KVIGTLKNSLFFSAQPFEITASTNNEG <del>N</del> LKVRFPLRLTGKIDFLNNYALFLSPSAQQASW	Human (3001-3060)	
KVIGTLKNSLFSQAQP <del>F</del> MITASTNDGNLKVSFPLKL <del>T</del> GKIDFLNNYALFLSPHAQQASW	Hamster (frag 1)	
KVIGTLKNSLFFSAQPFEITASTNNEG <del>N</del> LKVGFPLKL <del>T</del> GKIDFLNNYALFLSPRAQQASW	Mouse (frag 1)	

FIG. 14B

48/56

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SF ID NO:216 apoB-100 Sequence

QVSARFNQYKYNQNFSAGNNENIMEAHVGINGEANLDFLNIPPLTIPEMRLPYTIIITPPPL	Human (3061-3120)
QVSARFNQYKYNQNFSAINNEHNIEAHVGMINGDANLDFLTIPPLTIPEVKLPYIGLTTPLL	Hamster (frag 1)
QASTRFNQYKYNQNFSAINNEHNIEASIGMINGDANLDFLNIPPLTIPEINLPYTFKTPLL	Mouse (frag 1)
KDFSLWEKTKGLKEFLKTTKQSFDL SVKAQYKKNNKHRHSITNPLAVLCEFISQSISIKSFDRH	Human (3121-3180)
KDFSIWEETGLK-----KQSFDL SVKAQYKKNNDRHSIAIPLNGFYEFILNNVDSGIGK	Hamster (frag 1)
KDFSIWEETGLKKEFLKTTKQSFDL SVKAQYKKNSDKHSIVVPLGMFYEFILNNVNSWDRK	Mouse (frag 1)
FEKNRNNALDFVTKSNETKIKFDKYKAESQDELPRTFQIPGYTVPVNNEVSPFTIEM	Human (3181-3240)
IGKVVRDSDLYLISSYNEAKNNKFEN-----SLIQPSRTFQKRGYTIPFVNIEVTPFTVET	Hamster (frag 1)
FEKVRNNALHFLLTTSYNEAKIKVDKYKTENSLNQPSGTFQNHGYTIPFVNIEVSPFAVET	Mouse (frag 1)
SAGFYVFPKAWSMPSFSILGSDVRVPSYTL ILPSLELPVLHVPRNL -KLSSLPHFKELCTIS	Human (3241-3300)
LASSHVIPKAINTPSVHILGPNVIVPSYRL VLPSELPLVLRVPRNLLKFSLPDFKELRTID	Hamster (frag 1)
LASRHHVIPTAISTPSVТИPGNIMWPSYKL VLPPPLELPVFHGPGNLFKKFLPDFKGFTNTID	Mouse (frag 1)
HIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLLSSSSVIDALQYKLEGITTRL	Human (3301-3360)
NIYIPALGNFTYDFSFKSSVITLNTNVGL YNRS DIVAHFLSSSSFVTDALQYKLEGTSRL	Hamster (frag 1)
NIYIPAMGNFTYDFSFKSSVITLNTNAGLYNQSDIVAHFLSSSSVTDALQYKLEGTSRL	Mouse (frag 1)
TRKRGLKLATALSLSNKFVEGSHNSTVSL TTTKNMEVSAKTTKAEI -PILRMNFKQELNGN	Human (3361-3420)
TRKRGLKLATALDSL TNKFVKGHNHDSTFSL TKKNMEASV-KTT -ANL HAPILTMMNFKQELNGN	Hamster (frag 1)
MRKRGLKLATALAVSL TNKFVKGSHDSTISL TKKNMEASV-RTT -ANL HAPIFMSMFKQELNGN	Mouse (frag 1)

FIG. 14C

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SF  
ID NO:216 apoB-100 Sequences

<u>T</u> <u>K</u> <u>S</u> <u>K</u> <u>P</u> <u>T</u> <u>V</u> <u>S</u> <u>S</u> <u>M</u> <u>E</u> <u>F</u> <u>K</u> <u>Y</u> <u>D</u> <u>F</u> <u>N</u> <u>S</u> <u>M</u> <u>L</u> <u>Y</u> <u>S</u> <u>T</u> <u>A</u> <u>K</u> <u>G</u> <u>A</u> <u>V</u> <u>D</u> <u>H</u> <u>K</u> <u>L</u> <u>S</u> <u>L</u> <u>E</u> <u>S</u> <u>L</u> <u>T</u> <u>S</u> <u>Y</u> <u>F</u> <u>S</u> <u>I</u> <u>E</u> <u>S</u> <u>S</u> <u>T</u> <u>K</u> <u>G</u> <u>D</u> <u>V</u> <u>K</u> <u>G</u> <u>S</u> <u>V</u> <u>L</u> <u>S</u> <u>R</u>	Human (3421-3480)
<u>A</u> <u>K</u> <u>S</u> <u>K</u> <u>P</u> <u>I</u> <u>V</u> <u>S</u> <u>S</u> <u>I</u> <u>E</u> <u>L</u> <u>N</u> <u>D</u> <u>F</u> <u>N</u> <u>S</u> <u>S</u> <u>K</u> <u>L</u> <u>Y</u> <u>S</u> <u>T</u> <u>A</u> <u>K</u> <u>G</u> <u>G</u> <u>V</u> <u>D</u> <u>H</u> <u>K</u> <u>F</u> <u>S</u> <u>L</u> <u>E</u> <u>S</u> <u>L</u> <u>T</u> <u>S</u> <u>Y</u> <u>F</u> <u>S</u> <u>I</u> <u>E</u> <u>S</u> <u>S</u> <u>T</u> <u>K</u> <u>G</u> <u>N</u> <u>I</u> <u>K</u> <u>G</u> <u>S</u> <u>V</u> <u>L</u> <u>S</u> <u>Q</u>	Hamster (frag 1)
<u>T</u> <u>K</u> <u>S</u> <u>K</u> <u>P</u> <u>T</u> <u>V</u> <u>S</u> <u>S</u> <u>I</u> <u>E</u> <u>L</u> <u>N</u> <u>D</u> <u>F</u> <u>N</u> <u>S</u> <u>S</u> <u>K</u> <u>L</u> <u>H</u> <u>S</u> <u>T</u> <u>A</u> <u>T</u> <u>G</u> <u>G</u> <u>I</u> <u>D</u> <u>H</u> <u>K</u> <u>F</u> <u>S</u> <u>L</u> <u>S</u> <u>Q</u>	Mouse (frag 1)
<u>E</u> <u>Y</u> <u>S</u> <u>G</u> <u>T</u> <u>I</u> <u>A</u> <u>S</u> <u>E</u> <u>A</u> <u>N</u> <u>T</u> <u>Y</u> <u>L</u> <u>N</u> <u>S</u> <u>K</u> <u>S</u> <u>T</u> <u>R</u> <u>S</u> <u>S</u> <u>V</u> <u>K</u> <u>L</u> <u>Q</u> <u>G</u> <u>T</u> <u>S</u> <u>K</u> <u>I</u> <u>D</u> <u>I</u> <u>W</u> <u>N</u> <u>L</u> <u>E</u> <u>V</u> <u>K</u> <u>E</u> <u>N</u> <u>F</u> <u>A</u> <u>G</u> <u>E</u> <u>A</u> <u>T</u> <u>L</u> <u>Q</u> <u>R</u> <u>I</u> <u>Y</u> <u>S</u> <u>L</u> <u>W</u> <u>E</u> <u>H</u> <u>S</u> <u>T</u>	Human (3481-3540)
<u>E</u> <u>Y</u> <u>S</u> <u>G</u> <u>S</u> <u>V</u> <u>A</u> <u>S</u> <u>E</u> <u>A</u> <u>N</u> <u>T</u> <u>Y</u> <u>L</u> <u>N</u> <u>S</u>	Hamster (frag 1)
<u>E</u> <u>Y</u> <u>S</u> <u>G</u> <u>S</u> <u>V</u> <u>A</u> <u>N</u> <u>E</u> <u>A</u> <u>N</u> <u>V</u> <u>Y</u> <u>L</u> <u>N</u> <u>S</u>	Mouse (frag 1)

FIG. 14D

50/56

Alignment of Human 3481-4536 SEQ ID NO:217 with Rat SEQ ID NO:218 apoB-100 Sequence

EYSGTIAEANTYLNSKSTRSSVKLQGTSKIDDIWNLEWKENFAGEATLQR <del>IYSLWEHST</del>	Human (3481-3540)
<del>NSKGTRSSVRLQGASNFAGIWNFEVGENFAGEATLRR<del>IYGTWEHNM</del></del>	Rat ( frag 2)
<del>KNHLQLEGGLFTNGEHTSKATLIELSPWQMSALVQVHASQPSFFHD<del>DFPD</del>LGQEVALNANTK</del>	Human (3541-3600)
<del>TINHLQVF SYFDT<del>K</del>GKQTCRATLELSPTMSTLLQVHV<del>SQPSPL</del>FDLHHF DQEVLKASTK</del>	Rat ( frag 2)
<del>NQKIRW<del>K</del>NERVIHSGSFQSQVELSNDQEEKAHLDIAGSLEGH<del>L</del>RFLKNIILPVYDKSLWDF</del>	Human (3601-3660)
<del>NQKV<del>SWK</del>SEVQVESQWLQHNAHFSNDQEEVRLDIAGSLEG</del>	Rat ( frag 2)
-----	Human
ENFFLPAFGKS-----	Rat ( frag 2)
-----	Human (3661-3720)
<del>LKLDVTTSIGRRQH<del>LRV</del>STAFVYTKNPNGYSFSIIPVKVLADKFITPGLKLNDLNSVLVMP</del>	Rat ( frag 2)
<del>LR-ELLQIDGKRQY<del>Y</del>LQ<del>A</del>STSLHYTKNPNGYLLSLPVQELTDRF<del>I</del>IPGLKLNDF-----</del>	Human (3721-3780)
<del>TFHVPFTDLQVPSCKLDFREIQIYKKLRTSSFA<del>N</del>LPTEVKFPEVDVLTKYSQPEDSL</del>	Rat ( frag 2)
<del>-----SGIKIYKKLSTSPF<del>A</del>LN<del>T</del>MLPKVKFPGVDLLTQYSKPEGSS</del>	Human (3781-3840)
<del>IPFFEITV<del>P</del>ESQLTV<del>S</del>RFTLPKSVSDGIAALDLNAVANKIADFELPTIIIVPEQTIEIPSI</del>	Rat ( frag 2)
<del>VPTFETTIPEIQLTVSQFTLP<del>K</del>SFPVGNTVFDLNKL<del>T</del>NLIADVDLPSITLPEQTIEIPSL</del>	Human (3841-3900)
<del>KFSVPAGIVIPS<del>F</del>QALTARFEWDS<del>P</del>VYNATWSASL<del>K</del>KNKADYVETVLD<del>D</del>STCSSTLQFLEYA</del>	Rat ( frag 2)

51/56

Alignment of Human [348] -4536 SEO ID NO:217 with Rat SEO ID NO:218 apoB-100

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FIG. 14E

Alignment of Human 3481-4536 SEQ ID NO:217 with Rat SEQ ID NO:218 apoB-100  
Sequences

<u>LKE</u> N <u>C</u> <u>NLH</u> <u>KF</u> <u>NE</u> <u>F</u> <u>I</u> <u>Q</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>E</u> <u>A</u> <u>S</u> <u>Q</u> <u>E</u> <u>L</u> <u>Q</u> <u>I</u> <u>H</u> <u>Q</u> <u>Y</u> <u>I</u> <u>M</u> <u>A</u> <u>R</u> <u>E</u> <u>E</u> <u>Y</u> <u>F</u> <u>D</u> <u>P</u> <u>S</u> <u>I</u> <u>V</u> <u>G</u> <u>M</u> <u>T</u> <u>V</u> <u>K</u> <u>Y</u> <u>Y</u> <u>E</u> <u>E</u> <u>E</u> <u>K</u> <u>I</u>	Human (4321-4380)
<u>L</u> <u>R</u> <u>E</u> <u>N</u> <u>I</u> <u>Y</u> <u>S</u> <u>V</u> <u>F</u> <u>S</u> <u>E</u> <u>F</u> <u>N</u> <u>D</u> <u>F</u> <u>V</u> <u>Q</u> <u>S</u> <u>I</u> <u>L</u> <u>Q</u> <u>E</u> <u>G</u> <u>S</u> <u>Y</u> <u>K</u> <u>L</u> <u>Q</u> <u>Q</u> <u>V</u> <u>H</u> <u>Q</u> <u>Y</u> <u>M</u> <u>K</u> <u>A</u> <u>F</u> <u>R</u> <u>E</u> <u>E</u> <u>Y</u> <u>F</u> <u>D</u> <u>P</u> <u>S</u> <u>V</u> <u>V</u> <u>G</u> <u>M</u> <u>T</u> <u>V</u> <u>K</u> <u>Y</u> <u>Y</u> <u>E</u> <u>E</u> <u>K</u> <u>M</u>	Rat (frag 2)
<u>V</u> <u>S</u> <u>L</u> <u>I</u> <u>K</u> <u>N</u> <u>L</u> <u>V</u> <u>A</u> <u>L</u> <u>K</u> <u>D</u> <u>F</u> <u>H</u> <u>S</u> <u>E</u> <u>Y</u> <u>I</u> <u>V</u> <u>S</u> <u>A</u> <u>S</u> <u>N</u> <u>F</u> <u>T</u> <u>Q</u> <u>S</u> <u>L</u> <u>S</u> <u>S</u> <u>Q</u> <u>V</u> <u>E</u> <u>Q</u> <u>F</u> <u>L</u> <u>H</u> <u>R</u> <u>N</u> <u>I</u> <u>Q</u> <u>E</u> <u>Y</u> <u>L</u> <u>S</u> <u>I</u> <u>L</u> <u>T</u> <u>D</u> <u>P</u> <u>D</u> <u>G</u> <u>K</u> <u>G</u> <u>E</u> <u>K</u> <u>I</u> <u>A</u>	Human (4381-4440)
<u>V</u> <u>D</u> <u>L</u> <u>I</u> <u>K</u> <u>T</u> <u>L</u> <u>A</u> <u>P</u> <u>L</u> <u>R</u> <u>D</u> <u>F</u> <u>Y</u> <u>S</u> <u>E</u> <u>Y</u> <u>S</u> <u>V</u> <u>T</u> <u>A</u> <u>A</u> <u>D</u> <u>F</u> <u>A</u> <u>S</u> <u>K</u> <u>M</u> <u>S</u> <u>T</u> <u>Q</u> <u>V</u> <u>E</u> <u>Q</u> <u>F</u> <u>V</u> <u>S</u> <u>R</u> <u>D</u> <u>I</u> <u>R</u> <u>E</u> <u>Y</u> <u>L</u> <u>S</u> <u>M</u> <u>L</u> <u>A</u> <u>D</u> <u>I</u> <u>N</u> <u>G</u> <u>K</u> <u>G</u> <u>R</u> <u>E</u> <u>K</u> <u>V</u> <u>A</u>	Rat (frag 2)
<u>E</u> <u>L</u> <u>S</u> <u>A</u> <u>T</u> <u>Q</u> <u>E</u> <u>I</u> <u>I</u> <u>K</u> <u>S</u> <u>Q</u> <u>A</u> <u>I</u> <u>A</u> <u>T</u> <u>K</u> <u>K</u> <u>I</u> <u>I</u> <u>S</u> <u>D</u> <u>Y</u> <u>H</u> <u>Q</u> <u>F</u> <u>R</u> <u>Y</u> <u>K</u> <u>L</u> <u>Q</u> <u>D</u> <u>F</u> <u>S</u> <u>D</u> <u>Q</u> <u>L</u> <u>S</u> <u>D</u> <u>Y</u> <u>Y</u> <u>E</u> <u>K</u> <u>F</u> <u>I</u> <u>A</u> <u>E</u> <u>S</u> <u>K</u> <u>R</u> <u>L</u> <u>I</u> <u>D</u> <u>S</u> <u>I</u> <u>Q</u> <u>N</u>	Human (4441-4500)
<u>E</u> <u>L</u> <u>S</u> <u>I</u> <u>V</u> <u>V</u> <u>K</u> <u>E</u> <u>R</u> <u>I</u> <u>K</u> <u>S</u> <u>W</u> <u>S</u> <u>T</u> <u>A</u> <u>V</u> <u>E</u> <u>I</u> <u>T</u> <u>S</u> <u>D</u> <u>Y</u> <u>L</u> <u>R</u> <u>Q</u> <u>L</u> <u>H</u> <u>S</u> <u>K</u> <u>L</u> <u>Q</u> <u>D</u> <u>F</u> <u>S</u> <u>D</u> <u>Q</u> <u>L</u> <u>S</u> <u>G</u> <u>Y</u> <u>Y</u> <u>E</u> <u>K</u> <u>F</u> <u>V</u> <u>A</u> <u>E</u> <u>S</u> <u>T</u> <u>R</u> <u>L</u> <u>I</u> <u>D</u> <u>S</u> <u>I</u> <u>Q</u> <u>N</u>	Rat (frag 2)
<u>Y</u> <u>H</u> <u>T</u> <u>F</u> <u>L</u> <u>I</u> <u>I</u> <u>T</u> <u>E</u> <u>L</u> <u>K</u> <u>K</u> <u>L</u> <u>Q</u> <u>S</u> <u>T</u> <u>T</u> <u>V</u> <u>M</u> <u>N</u> <u>--</u> <u>P</u> <u>Y</u> <u>M</u> <u>K</u> <u>L</u> <u>A</u> <u>P</u> <u>G</u> <u>E</u> <u>L</u> <u>T</u> <u>I</u> <u>I</u> <u>L</u>	Human (4501-4536)
<u>Y</u> <u>H</u> <u>M</u> <u>F</u> <u>L</u> <u>R</u> <u>Y</u> <u>I</u> <u>A</u> <u>E</u> <u>L</u> <u>L</u> <u>K</u> <u>K</u> <u>L</u> <u>Q</u> <u>V</u> <u>A</u> <u>T</u> <u>A</u> <u>N</u> <u>N</u> <u>V</u> <u>S</u> <u>P</u> <u>Y</u> <u>L</u> <u>R</u> <u>F</u> <u>A</u> <u>Q</u> <u>G</u> <u>E</u> <u>L</u> <u>I</u> <u>I</u> <u>F</u>	Rat (frag 2)

FIG. 14G

Alignment of Human 4141-4536 SEQ ID NO:219 with Chicken SEQ ID NO:220 apoB-100 Sequences

<u>KDNVFDGLVRVTQKFHMKVKHLIDSLIDFLNFPRFQFPGKPGIY</u>	<u>TREELCTMFI</u>	<u>REVGT</u>	Human (4141-4200)
<u>VQLSEK</u>	<u>YRLLKDL</u>	<u>SKEAEQEVFKAI</u>	Chicken (frag 1)
<u>LSQVYSKVHNGSEILFSYFQLVITLPPFELRKHKLI</u>	<u>IDVISMYRELLKDL</u>	<u>SKEAEQEVFKAI</u>	Human (4201-4260)
<u>ADICLSSLQEYFDALIAAISELEV</u>	<u>RVPASETILRGRNVLDQIKEML</u>	<u>KHLQEKIRQTFVTL</u>	Chicken (frag 1)
<u>OSLKTTEVLRNQLDQQIFFQLIEDNIKQLKEMKFTYLINYIQDEINTIFNDYIPYVFKL</u>	<u>YKQMQQLYK</u>	<u>DAMASDYAHKLRS</u>	Human (4261-4320)
<u>QEADFAAGKLNRKLQVVQVKTFQKAGNMVRSLQS</u>	<u>KNFEDIKVQM</u>	<u>QQLYKDA</u>	Chicken (frag 1)
<u>LKENLCLNLHKFNEFIFIQNELQEAQELQOIHQYIMALREEYFDP</u>	<u>PSIVGWTVKYYELEEKI</u>	<u>I</u>	Human (4321-4380)
<u>LAENVKKYISQIKNFSQKTLQKLSENLQLQLVLYIKALREEYFDPTTLGSV</u>	<u>VKYYEVEDKV</u>	<u>I</u>	Chicken (frag 1)
<u>VSLIKNLVALKDFHSEYIVSASNFTSQLSSQEQLFLHRN</u>	<u>IQEYLSILTDPDGKGKEKIA</u>	<u>IA</u>	Human (4381-4440)
<u>GLLKNLMDTLVIMWNEYAKDLSDLVTRLTDQVRELVENYRQ</u>	<u>QEYYDLITDVEGKGGRQKWM</u>	<u>W</u>	Chicken (frag 1)
<u>ELSATAQEIIKSQAIATKKIISDYHQHQFRYKLQDFSDQLSDYYEKFIAESKRLIDL</u>	<u>SIGN</u>	<u>Q</u>	Human (4441-4500)
<u>ELSSAAQEKIRYWMSAVAKRKINEHNRQVKAKLQEIYGQLSDSQEKLINVAKMLIDL</u>	<u>TVEK</u>	<u>V</u>	Chicken (frag 1)
<u>YHTFLIYITELLKKLQSTTVMNYPM</u>	<u>KLAPGELTIIL</u>	<u>--</u>	Human (4501-4536)
<u>YSTFMKYIFELLRWFEQATADS</u>	<u>IKPYIAVREGELRIDVPDFWEYINQMPQKSREALRNKV</u>	<u>--</u>	Chicken (frag 1)
<u>ELTRALIQQGVEQGTRKWEEMQAFIDEQLATEQLSFQQIVENIQKRMKT</u>	<u>--</u>	<u>--</u>	Human
<u>--</u>	<u>--</u>	<u>--</u>	Chicken (frag 1)

FIG. 14H

54/56

Alignment of Human 1561-1740 SEQ ID NO:221 with Rabbit SEQ ID NO:222 apoB-100

Sequences			
DMTFSKQNALLRSEYQADYESLRFSSLLSGSLNSHGLELNADILGTDK <u>INSGAHKATLRI</u>	Human (1561-1620)		
DLTFSKQNALLR <del>A</del> EYQADYKSLRFFTLLSGLLNTHGLELNADILGTDK <u>MNTAAHKATLRI</u>	Rabbit (frag 1)		
GQDGISTSATTNL <u>KCSLLVLENELMELGSGASMKLT</u> TNGRFREHNAKFSLDGKAALTE	Human (1621-1680)		
GQNGVSTSATTSL <u>RYSPML</u> ENELMELGSGASMKLA <u>TNGRFKEHNAKFSLDGKATLTE</u>	Rabbit (frag 1)		
LSLGSAYQAMILGVDSKNIFNFKV <u>SQEGLKL</u> SNDMMGSYAEMKFDHTNSLNIAGL SLD <del>FS</del>	Human (1681-1740)		
LSLGSAYQAMILGADS <u>KNIFNF</u> -----	Rabbit (frag 1)		

55/56

Alignment of Human 3301-3720 SEQ ID NO:223 with Rabbit SEQ ID NO:224 apoB-100  
 Sequences

<u>HIFIPAMGNITYDFSFKSSVITLN</u>	<u>NTNAELFNQSDIVAHLL</u>	<u>SSSSVIDALQYKLEGTTRL-</u>	Human (3301-3360)
<u>TRKRGLKLATALSINKFVEGSHN</u>	<u>STVSLTTK</u>	<u>NMEVSVAKTTKAEIFIILRMNFKQELNGN</u>	Rabbit (frag 2)
<u>RRRI-----EPWEFEVFFDPQELR</u>	<u>KEA</u>	<u>CLLYEIKWGASSKTWRSSGKNTTNH-VEVN</u>	Human (3361-3420)
-----	-----	-----	Rabbit (frag 2)
FLEKLT	-----	-----	Human (3421-3480)
TKSKPTVSSSMEFKYDFNSSMILYSTAKGAVDHKL	SLES	TSYFSESSTKGDVKGSVLSR	Rabbit (frag 2)
-----	-----	-----	Human (3481-3540)
EYSGTIASEANTYLN	SKSTRSSVKL	I QGTSKIDDIWNLLEVKENFAGEATLQRIYSLWEHST	Rabbit (frag 2)
RKEACLLYEIKWGA	SSKTWRSSGK	-NTTNHVEVNF-LE-KLTSEGRLGPSTCCSI-----	Human (3541-3600)
-----	-----	-----	Rabbit (frag 2)
KNHLQLEGLFFTNGEHTSKATL	ELSPWQMSA	VQVHASQOPSSFHDFPDLGQEVALNANTK	Human (3601-3660)
TWFLSWs	-----	-----	Rabbit (frag 2)
NQKIRWKNEVRIHSGSFQSQVELSNDQEAHLDIAGSLEGHLRF	LFKNIIIPVYDKSLWDF	-----	Human (3661-3720)
WMSVSEYC	CWENFVNYP	PPGKAAQWPRYPPRWMMLMYALELYCIIILGLPPC-----	Rabbit (frag 2)
LKDVTTSIGRRQHL	RVSTAFVYTKNPNGYSFSIPVKVLADKFITPGKL	NDLNSVLVMP	-----
-----	-----	-----	Rabbit (frag 2)
LKISRRHQKQL	-----	-----	-----

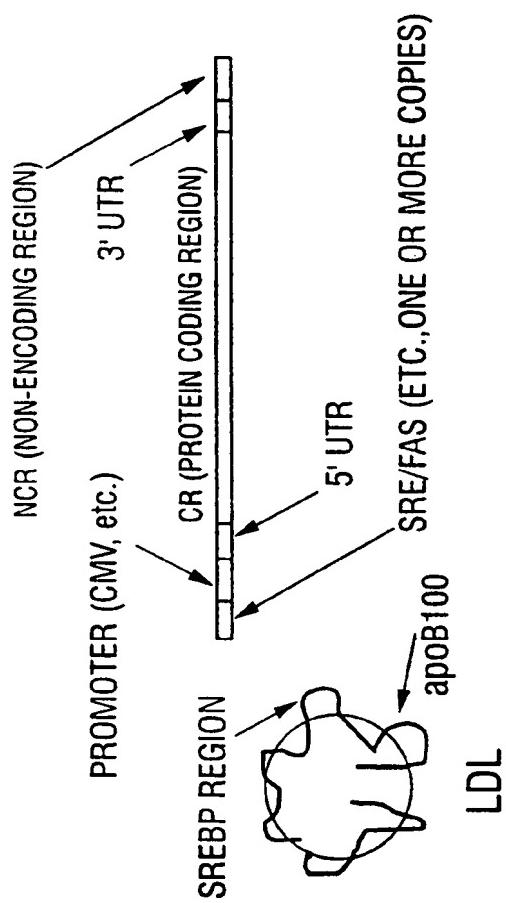


FIG. 15

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/11927

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C12N15/87 C07K14/775 A61K47/48 A61K48/00

According to International Patent Classification(IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIM J.S. ET AL.: "Terplex system of lipoprotein, cationic polymer and DNA for gene delivery" PHARM. RES., vol. 12, no. 9 suppl., 1995, page S80 XP002079291 see abstract ---	1, 4, 5, 20, 40, 44, 45, 64-66
A	WO 87 02061 A (BIOTECH RES PARTNERS LTD) 9 April 1987 see abstract see page 1 - page 3 see example 1 ---	1-65
A	WO 93 04701 A (UNIV CONNECTICUT) 18 March 1993 see abstract see page 5, line 17 - page 8, line 3 ---	1-65
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 October 1998

Date of mailing of the international search report

13/10/1998

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Galli, I

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 98/11927

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 31557 A (CLONEXPRESS INC) 23 November 1995 see abstract see table 1 ---	1-65
A	WO 95 28494 A (TARGETED GENETICS CORP ;OVERELL ROBERT W (US); WEISSER KAREN E (US) 26 October 1995 see abstract ---	1-65
A	BLACKHART B.D. ET AL.: "An expression system for human apolipoprotein B 100 in a rat hepatoma cell line" J. BIOL. CHEM., vol. 265, no. 15, 25 May 1990, pages 8358-8360, XP002079292 see the whole document ---	1-65
A	KANEDA Y ET AL: "INCREASED EXPRESSION OF DNA COINTRODUCED WITH NUCLEAR PROTEIN IN ADULT RAT LIVER" SCIENCE, vol. 243, 20 January 1989, pages 375-378, XP000602256 see the whole document ---	1-65
A	GUEVARA J. ET AL.: "Evidence that ApoB100 of LDL is a novel Src-related protein kinase." J. PROT. CHEM., vol. 14, no. 7, 1995, pages 627-631, XP002079293 see abstract ---	1-65
P,X	WO 98 00556 A (UNIV UTAH RES FOUND) 8 January 1998  see abstract see figure 1 -----	1,4,5, 20,40, 44,45, 64-66

## INTERNATIONAL SEARCH REPORT

It is a national application No.

PCT/US 98/11927

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 53 - 63 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking(Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 98/11927

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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WO 9531557	A 23-11-1995	US CA EP JP	5670347 A 2189975 A 0759996 A 10500022 T	23-09-1997 23-11-1995 05-03-1997 06-01-1998
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